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(Continued)

THE VEGETABLE GUMS BY INGESTION IN THE ETIOLOGY OF ALLERGIC DISORDERS*†

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THE vegetable gums as causative factors in allergic disturbances, by means of inhalation, surface contact, and injection, have been recorded by various investigators[1-7] including the present writer.[11] The present paper stresses the importance of these gums as agents that cause allergic symptoms by ingestion.

Ivy and Isaacs' report[8] of the effect of the laxative Mucara which contains karaya should be mentioned here. In a group of eighty-nine test subjects, 7.8 per cent complained of mild abdominal cramps or other discomfort after the ingestion of this laxative.

Figley[9] observed sixteen women with allergic symptoms, all of whom gave positive reactions to scratch tests with karaya. The family histories for allergy were positive in all but two of these subjects. The allergens had been absorbed by ingestion and by surface contact, as well as by inhalation. The chief manifestations were perennial rhinitis, asthma, atopic dermatitis, urticaria, and gastrointestinal distress. Wave lotions, laxatives, emulsified mineral oil, gelatins, diabetic foods, tooth pastes, and denture adhesive powders were the sources of sensitization.

The first case report of an allergic reaction by ingestion, to drug tablets containing the vegetable gums, was presented by Brown and Crepea.[10] This was a white man who manifested symptoms of asthma and generalized urticaria from the ingestion of Pyribenzamine tablets which contain tragacanth. Skin tests, passive transfer, and clinical trial established this vegetable gum as the cause.

Further proof of the role of the vegetable gums, by ingestion, in the causation of allergic disorders will form the basis of the present paper. In Table I is recorded a series of ten subjects suffering from allergic disorders caused by the ingestion of foods which contained karaya, tragacanth, or arabic. Direct

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TABLE I. ALLERGIC DISORDERS IN TEN SUBJECTS RESULTING FROM INGESTION OF FOODS CONTAINING THE VEGETABLE GUMS

CASE AND SUBJECT	AGE AND SEX	GUM-CONTAINING FOODS CAUSING SYMPTOMS	CLINICAL MANIFESTATIONS OF ALLERGY	SKIN-REACTING GUMS	OTHER ALLERGENIC SENSITIVITIES OF IMPORTANCE
1. R. L.	22 F.	Cream cheese, fillings in candies, marshmallows	Vasomotor rhinitis, gastrointestinal symptoms, epigastric distress, nausea, belching, flatulence	Karaya *Tragacanth** Arabic	Dust
2. L. K.	11 M.	Commercially prepared pie crust mixtures, marshmallows, certain brands wheat cakes, certain brands cream cheese, commercially prepared cake icing, gelatine	Vasomotor rhinitis, gastrointestinal symptoms, urticaria, allergic cough	Arabic Karaya	Dust, animal epithelia, orris root, cotton, silk, chocolate, fish, paprika, mushroom
3. S. S.	35 M.	Commercially prepared white sauce, commercially prepared mustard, processed cheddar cheese, processed Swiss cheese, commercially prepared potato salad	Urticaria, angioedema	Tragacanth Arabic	Dust
4. R. B. A.	37 F.	Commercially prepared cake icing, commercially prepared whipped cream, ice cream mixtures	Vasomotor rhinitis	Karaya Arabic	Dust
5. J. G.	29 M.	Commercially prepared cake icing, fillings in candies, cream cheese	Gastrointestinal allergy: epigastric distress, belching, flatulence, diarrhea	*Karaya* *Tragacanth* Arabic	Dust, animal epithelia, tobacco, timothy, ragweed, mushroom, spinach, banana
6. A. S.	13 M.	Certain brands of tooth paste	Vasomotor rhinitis: clogged nose, running nose, sneezing	*Arabic* Karaya Tragacanth	Dust
7. M. G.	45 M.	Certain brands of gum	Bronchial asthma	Tragacanth Arabic	Trees, grasses, ragweed, dust
8. G. C.	35 M.	Gelatines, commercial whipped cream in "charlotte russe," fillings in candies	Urticaria, angioedema, itchy gums	Karaya Tragacanth Arabic	Dust, trees, ragweed, animal epithelia
9. B. D.	16 F.	Ice cream mixture, frozen custard	Vasomotor rhinitis, bronchial asthma	*Karaya* *Tragacanth* Arabic	Dust, trees, grasses, ragweed, animal epithelia
10. L. D.	55 M.	Commercially prepared salad dressings, shrimp sauce and other white sauces	Vasomotor rhinitis: nasal congestion, rhinorrhea, clogged nose, sneezing	Karaya Tragacanth *Arabic*	Trees, grasses, dust, chocolate, orange

*Italics denotes dominant reactor or reactors.

SUMMARY OF TABLE I

TOTAL NO. OF SUBJECTS	AGE RANGE	NUMBER OF INDIVIDUAL FOODS CONTAINING THE GUMS	TOTAL NUMBER OF ALLERGIC MANIFESTATIONS	NUMBER GIVING POSITIVE SKIN REACTIONS TO THE GUMS		
				KARAYA	ARABIC	TRAGACANTH
10 7 males 3 females	11-55 years	19	7	8	10	8
		Cake icing (commercially prepared) Cheddar cheese (processed) Cream cheese Fillings in candies Frozen custard Gelatins Gum (certain brands) Ice cream mixtures Gelatin Marshmallows Mustard (commercially prepared) Pie crust (commercially prepared) Potato salad (commercially prepared) Salad dressings (commercially prepared) Shrimp sauce (commercially prepared) Swiss cheese (processed) Tooth paste (certain brands) Wheat cakes (certain brands) Whipped cream (commercially prepared) White sauce (commercially prepared)	Bronchial asthma Allergic cough Angioedema Gastrointestinal allergy Urticaria Vasomotor rhinitis Itchy gums			

skin tests with the gums, clinical trial and elimination, and positive serologic findings confirmed these suspicious allergens as the causative agents. The allergic manifestations recorded in Table I were not only gastrointestinal reactions but consisted also of many other systemic reactions of allergy such as bronchial asthma, generalized urticaria, vasomotor rhinitis, and so forth. Elimination of the suspected irritant foods obviated the symptoms. Clinical trial repeatedly reproduced these symptoms.

SEROLOGIC STUDIES

Four sera in this group were found to contain abundant antibodies, and thus were suitable for passive transfer and neutralization studies. Results of these studies are shown in Tables II and III, respectively. The dominant gum antigens in these four subjects were: tragacanth and karaya in J. G. and B. D., and arabic in A. S. and L. D.

TABLE II. PASSIVE TRANSFER TESTS IN SERIAL DILUTIONS ON THE FOLLOWING GUM-SENSITIVE SERA

	These sites were tested 48 hrs. later with 1/40 to 1/20 c.c. of:		
1. J. G. serum.—Test sites of J. G. serum in serial dilutions were introduced into the back of a nonallergic donor	1% gum karaya	1% gum tragacanth	1% gum arabic
	Reactions		
Concentrate	marked	marked	marked
1 : 10	moderate	moderate	slight to moderate
1 : 100	slight	slight	negative
2. B. D. serum introduced in the same manner			
Concentrate	marked	marked	marked
1 : 10	slight	moderate to marked	slight
1 : 100	negative	slight	negative
3. A. S. serum introduced in the same manner			
Concentrate	moderate	moderate	marked
1 : 10	slight	slight	moderate
1 : 100	negative	negative	negative
4. L. D. serum introduced in the same manner			
Concentrate	moderate	moderate	marked
1 : 10	slight	slight to moderate	marked
1 : 100	slight	slight	slight

As can be seen from Table II, J. G., B. D., L. D., and A. S. showed strongly positive sera which transferred passively on a nonallergic donor.

From the neutralization studies, the following concrete conclusions may be drawn with respect to cross reactions between (1) tragacanth and karaya and (2) between tragacanth and arabic:

(1) In three of the four sera studied the evidence is presented that tragacanth neutralizes karaya. In one serum (J. G.) in which the addition of tragacanth to the serum failed to neutralize karaya, karaya was an unusual highly dominant clinical antigen in this subject.

(2) It was previously shown by the writer[11] that tragacanth neutralizes arabic, but arabic will not neutralize tragacanth. Apparently this pertains only in a serum in which tragacanth is the more dominant antigen. In the present study upon these highly gum-sensitive sera, it is evident that the clinical sensitivity dominance of either of these two antigens determines the capacity of one of them either to neutralize or not to neutralize its mate.

INGESTION OF THE POWDERED GUMS IN SENSITIVE SUBJECTS

Experimental Studies.—The vegetable gums, karaya, tragacanth, and arabic, were compounded in powder form, and 300 mg. of the mixed gums were calculated by weight to be contained in each powder. Four subjects (Cases 5, 6,

9, and 10) were fed powders containing these gums, and one subject (Case 1) was fed candies containing gum fillings. Results of these experiments were observed and recorded as follows:

Ingestion Experiment: Case 1 (R. L.)* had manifested the clinical forms of allergy as vasomotor rhinitis and gastrointestinal disturbance from the ingestion of foods containing vegetable gums. A brand of cream cheese, fillings in candies, and marshmallows were found to be the incriminating sources of allergic symptoms.

TABLE III. NEUTRALIZATION TESTS

	Three sites of .1 c.c. of each mixture for each serum were introduced into the skin of a nonallergic donor. After 48 hours these sites were tested with 1/40 to 1/20 c.c. of:		
A. Equal parts of J. G. serum and the three gum antigens of 1% concentration were mixed separately in vitro as well as equal parts of J. G. serum and saline as a control:*	1% gum karaya	1% gum tragacanth	1% gum arabic
	Reactions		
J. G. serum + karaya	slight	marked	moderate
J. G. serum + tragacanth	marked	moderate	moderate
J. G. serum + arabic	moderate	marked	slight
B. Same method of mixture, using B. D. serum as follows:			
B. D. serum + karaya	very slight	marked	moderate
B. D. serum + tragacanth	slight	moderate	negative
B. D. serum + arabic	moderate	marked	negative
C. Same method of mixture, using A. S. serum as follows:			
A. S. serum + karaya	very slight	moderate	marked
A. S. serum + tragacanth	negative	very slight	marked
A. S. serum + arabic	slight	slight	slight to negative
D. Same method of mixture, using L. D. serum as follows:			
L. D. serum + karaya	very slight	moderate	moderate to marked
L. D. serum + tragacanth	slight	very slight	marked
L. D. serum + arabic	slight	moderate	slight

*Serum plus saline controls were carried out in each of the four sera; the results resembled closely the serum dilution passive transfer tests given in Table II.

The following ingestion experiment was carried out in this subject: (This patient's favorite candies had been declared, by Dr. Pacini of Universal Colloid Company, to contain the vegetable gums.) For the experiment, Dr. Pacini arranged with a candy manufacturer to make up candies in two distinct layers. The top layer contained the vegetable gums, the bottom layer contained no vegetable gums. The patient, of course, had no knowledge of the contents of the candies. The layers were interchanged and fed to the patient at various intervals. Onset of the gastrointestinal symptoms in the form of belching, nausea, epigastric distress, and flatulence were invariably reported after ingestion of the candies containing vegetable gum fillings.

Ingestion Experiment: Case 5 (J. G.)* had been found markedly sensitive to karaya, tragacanth, and arabic. Trial and error methods disclosed the fact

*See Table I.

that ingestion of certain commercially prepared cake icings, certain fillings in candies, and certain brands of cream cheese known to contain the vegetable gums had invariably resulted in symptoms of epigastric distress, belching, flatulence, and a most disturbing severe diarrhea.

The following experiment was undertaken: The patient was given powders each containing 300 mg. of the mixed gums, namely, karaya, tragacanth, and arabic, to be taken every two hours. Six hours after the initial ingestion of the powders (after an intake of 900 mg.) there resulted a soft stool. After an intake of 1,200 mg. there resulted a definite diarrhea; there were also associated symptoms of epigastric distress, belching and flatulence. A single dose of 2,100 mg. of the powders produced, within three hours, all of the symptoms stated above.

Ingestion Experiment: Case 9 (B. D.)* had been found markedly sensitive to karaya, tragacanth, and arabic. Ingestion of ice cream and frozen custard known to contain the vegetable gums produced symptoms of vasomotor rhinitis and bronchial asthma. Ingestion of the same foods free from the vegetable gums was normally tolerated.

The following experiment was carried out: on the morning of June 5, 1948, the patient was given powders, each containing 300 mg. of mixed gums, namely, karaya, tragacanth, and arabic, every two hours. Soon after the intake of the powders, the patient suffered marked nasal congestion, rhinorrhea, and blocked nasal passages. After the third dose of the powders she sensed definite constriction in her chest, with audible wheezy respirations. Asthmatic breathing was marked at about 3 P.M. That afternoon the patient was forced to leave school and was confined to the house the rest of the day. She continued to take the powders in the late afternoon and, after having taken 1,500 mg., the symptoms of vasomotor rhinitis and bronchial asthma became markedly and progressively intensified. She was forced to resort to ephedrine sulfate capsules for relief of the symptoms.

Ingestion Experiment: Case 6 (A. S.)* had manifested symptoms of severe vasomotor rhinitis when applying certain brands of tooth paste as a dentifrice. The patient was found markedly sensitive by direct skin test and by passive transfer to the vegetable gums, karaya, tragacanth, and arabic.

The following experiment was carried out on this subject: At 5 P.M. of May 10th, the patient was given a total of 2,100 mg. of mixed gums in powder form, with one glass of water. At 5.20 P.M., there occurred marked clogging of the nose, continuous marked rhinorrhea and profuse discharge, and a good deal of sneezing. Examination of the nose revealed bilateral edema of the mucous membranes; the right inferior turbinate appeared greatly engorged and water-logged. There was marked obstruction on both sides of the nose due to the edema, rhinorrhea, and mucous discharge.

The control subject was G. L., 15 years of age. The skin test to karaya was 4 plus and to tragacanth and arabic, respectively, 2 plus and 1 plus. This subject gave a negative history regarding the ingestion of gum-containing foods. He was considered clinically nonsensitive to the gums.

*See Table I.

On the same day and at the same time the ingestion experiment was carried out on patient A. S., the control subject was given a similar amount of the gums (2,100 mg.) in powder form. The result was negative.

Ingestion Experiment: Case 10 (L. D.)* had been clinically sensitive to the following gum-containing foods: salad dressings, shrimp sauce, and other sauces known to contain the vegetable gums. The following events served as proof in this subject:

The direct skin test with karaya was moderate; to tragacanth, it was marked; and to arabic, it was markedly active.

TABLE IV. INGESTION EXPERIMENTS: SUMMARY TABLE

SUBJECT	AGE AND SEX	FEEDING METHOD EMPLOYED IN REPRODUCING SYMPTOMS	OTHER METHODS OF REPRODUCING SYMPTOMS	CLINICAL MANIFESTATIONS OF ALLERGY PRODUCED	TIME INTERVAL OF ONSET; DURATION OF SYMPTOMS
R. L.	22 F.	Vegetable gums in fillings of candies on top layer; no gums on bottom layer; layers interchanged	Feeding cream cheese containing gum, controlled by other types not containing gum, and marshmallows	Epigastric distress, belching, flatulence, nausea	Onset within minutes; lasted many hours
J. G.	29 M.	*May 28-29:* 300 mg. mixed gums in powder form every 2 hrs. Total: 1,200 mg. *June 10:* 2,100 mg. mixed gums in powder form, in one dose	Gum-containing cake icings, certain fillings in candies, certain brands of cream cheese	Epigastric distress, belching, flatulence, diarrhea	Onset within 4 to 6 hrs.; lasted 12 hrs.
A. S.	13 M.	2,100 mg. mixed gums, powder form, in one dose, with one glass of water	Certain brand of tooth paste	Severe acute symptoms of vasomotor rhinitis	Onset in 20 min.; lasted 1 hr.
B. D.	16 F.	300 mg. mixed gums in powder form every 2 hrs. Total: 1,500 mg.	Gum-containing ice cream, frozen custard	Vasomotor rhinitis, bronchial asthma	Onset within 6 hrs.; lasted 24 hrs.
L. D.	55 M.	2,100 mg. mixed gums in powder form with one glass of water	Gum-containing salad dressings, shrimp sauce, etc. Intradermal tests with the gums	Severe acute symptoms of vasomotor rhinitis	Onset within 10 min.; lasted 3 hrs.

In this summary table of the ingestion experiments we note particularly the following: in the cases of R. L., A. S., and L. D., the onset of symptoms occurred within minutes and lasted many hours in the first and last instances, and one hour in the case of A. S.

In the cases of J. G. and B. D., the onset of symptoms occurred within four to six hours, and lasted twelve hours in the former and twenty-four hours in the latter.

*See Table I.

On June 10, 1948, when tested intradermally with these gums for the first time, a reaction manifested itself in the form of severe vasomotor rhinitis, characterized by marked nasal congestion, rhinorrhea, clogging of the nasal passages, and severe sneezing. This reaction lasted three hours and was only slightly ameliorated by Trimeton.

On June 22, 1948, the patient was examined and his general condition was found excellent; the condition of the nose and throat were also excellent. He was again tested intradermally with karaya, tragacanth, and arabic. Reactions to the skin tests were positive, similar to the previous results, and a similar reaction, severe vasomotor rhinitis, resulted. This also lasted three hours.

On July 25, 1948, the patient was given 2,100 mg. of the mixed gums, karaya, tragacanth, and arabic, with a glass of water. A response similar to the above two reactions resulted.

TABLE V. RELATION OF THE DOMINANT ANTIGENS AS DETERMINED BY SEROLOGIC STUDIES AND DIRECT SKIN TESTS TO THE OBSERVED CLINICAL MANIFESTATIONS IN FIVE HIGHLY SENSITIVE SUBJECTS

SUBJECT	DOMINANT ANTIGEN BY DIRECT SKIN TEST	DOMINANT ANTIGEN BY SEROLOGIC RESULTS	CLINICAL MANIFESTATIONS
R. L.	Tragacanth	Not available	Gastrointestinal allergy
J. G.	Tragacanth Karaya	Tragacanth Karaya	Gastrointestinal allergy
A. S.	Arabic	Arabic	Vasomotor rhinitis
L. D.	Arabic	Arabic	Vasomotor rhinitis
B. D.	Karaya Tragacanth	Karaya Tragacanth	Bronchial asthma and vasomotor rhinitis

In four of these subjects, serologic studies were made, in addition to direct skin tests for the determination of the dominant antigen. In the two subjects with gastrointestinal allergy, tragacanth and karaya were the dominant antigens. In the two subjects with vasomotor rhinitis as the allergic manifestation, gum arabic was the dominant antigen; while in the one subject with bronchial asthma and an associated vasomotor rhinitis, karaya and tragacanth were the dominant antigens.

DISCUSSION

The present report deals with allergic disorders caused by the ingestion of the vegetable gums, karaya, tragacanth, and arabic. These gums were contained in certain brands of foods to add bulk, thickness, and binding qualities, for the purpose of "enriching" the foods and making them "heavy."

From the figures supplied by various importing houses[12] regarding the amount, in pounds, of these three gums consumed annually in the United States, it would appear that, if distributed equally per capita (on the basis of the 1940 census figures for the total population of the United States), there is a possibility that each person could be exposed to an average of 300 mg. of the gums, karaya, tragacanth, and arabic per day. Therefore in our ingestion experiments we used 300 mg. of the mixed gums in powdered form, and results obtained showed that very small amounts of these substances were capable of producing severe allergic symptoms. This fact has been previously reported.[10]

It is also possible that on certain days the gum intake from foods for certain individuals might be doubled or even tripled; for it may happen that on a

particular day an individual would include in his ingestion menu a complete five-cent package of gum drops, some gum-established ice cream, a gum-emulsified salad dressing, a gum-containing piping or icing, a gum-rich pie filler, and similar items for which the gums are used. This would naturally result in increased allergic symptoms and would account for gradations of symptomatology from the use of the gums in certain allergic patients.

Thus our patient J. G., who reacted with gastrointestinal symptoms from the gum-containing foods, would on some occasions have suffered only belching, epigastric distress and flatulence, and perhaps only a soft stool, while on other occasions a severe diarrhea would have been an additional symptom.

In a general way the major clinical manifestations of allergy resulting from the ingestion of the vegetable gums encountered in our ten subjects were bronchial asthma, urticaria, angioedema, vasomotor rhinitis, and gastrointestinal symptoms. There was no instance of migraine, acute or chronic eczema, or other manifestations of allergy traceable to the ingestion of the vegetable gums.

The four positive sera made available in the present series lent conclusive proof of the role of the gums as sensitizing allergens in predisposed persons, and served as a means in determining the dominant antigens in these subjects.

The vegetable gums employed otherwise than in foods were the subject of a previous study,[11] indicating their sensitizing qualities by inhalation and external contact. It should be stressed that a considerable amount of gum arabic finds its way into adhesives, and a considerable amount of gum tragacanth is used in cosmetic and pharmaceutical products; also that large quantities of karaya are contained in hair dressing, wave set, and other lotions employed for external application. In view of the wide usage of these gums, it is necessary to include them constantly in our testing tray.

Gums chemically similar to these principal commodities are frequently employed in their stead, such as cherry tree gum as a substitute for arabic, locust as a substitute for karaya, and algin and other gums as partial substitutes for tragacanth. Similarly, to counteract untoward reactions frequently occurring from laxatives, colloid laxatives are substituted at present. Synthetic mucilages such as polyvinyl alcohol and methyl cellulose are now employed to provide hydrophilic colloids which do not produce the usual side reactions of the vegetable gums. These hydrophilic colloids are not absorbed by the intestinal mucosa, are not degraded by intestinal enzymes, and are not antigenic.[13]

The following data regarding the use of the gums in the foods consumed by our patients has been supplied to the author and, by permission, are herewith listed:[14]

Gravies.—A frequent practice is that of adding gum tragacanth to impart thickening ordinarily achieved with flour and starches.

White Sauce.—As in the case of gravies, gum thickeners are used, principally tragacanth.

Prepared Mustard.—Some brands are thickened with karaya or locust to prevent separation.

Processed Cheddar Cheese.—Most processed cheeses contain gums, particularly karaya, locust, and, very rarely, tragacanth.

Processed Swiss Cheese.—See *Processed Cheddar Cheese.*

Prepared Potato Salad.—The dressing is thickened with karaya.

Cake Icing Mixtures.—These contain gum arabic and, less often, either karaya or locust.

Commercial Whipped Cream.—Frequently stabilized by a mixture of sugar, cornstarch, gelatin, agar-agar, salt, and vanilla. During the war, difficulty in procurement of agar led to its replacement in many instances by either karaya, locust, tragacanth, or, most generally, sodium alginate. This practice still persists.

Ice Cream Mixtures.—These contain karaya and/or locust. Sodium alginate is used in some, but karaya is more prevalent.

Fillings in Candies.—Soft centered candies usually contain considerable gum arabic. In some instances karaya is used.

Cream Cheese.—Packaged cream cheese is labeled with an indication that it carries a "vegetable stabilizer," most always karaya.

Tooth Paste.—Some tooth paste is free from gums, but some carry uronic acid gum, generally karaya and occasionally locust as a substitute for karaya.

Certain Brands of Chewing Gum.—The scarcity of chicle during the war resulted in the development of numerous gum substitutes, and in the change of several chewing gum formulas which included then (as many still include), gums such as tragacanth and, more rarely, karaya.

Charlotte Russe.—The whipped cream filling is stiffened with a gum, which replaces the agar-agar formerly used. Karaya is the commonest choice.

Shrimp Sauce.—See *White Sauce.*

Salad Dressing.—With the exception of mayonnaise, which would be considered adulterated by the Government if it contained gums, other forms of salad dressing substitutes for mayonnaise contain thickening agents, principally karaya, locust and, less frequently, tragacanth.

Marshmallows.—Ordinarily marshmallows are gelatine confections and are devoid of added gums. Occasionally, however, gum acacia is added. When marshmallows are prepared from *Althea officinalis*, it is a trade secret to employ gum acacia to insure the rigidity of the confection.

Certain Brands of Wheat Cakes.—Few prepared griddle cake flours disclose the presence of gum in the list of ingredients. Despite this, a number of prepared flours contain small amounts of the order of one-half per cent of karaya.

SUMMARY

1. The vegetable gums, tragacanth, karaya, and arabic, may cause allergic disorders by ingestion in sensitive subjects.

2. Ingestion experiments with these gums carried out in five sensitive subjects established the etiological relationship of these allergens to the allergic manifestations produced.

3. Passive transfer tests in serial dilutions as well as neutralization studies confirmed the allergenic nature of these gums in the sensitive subjects studied.

4. Widespread employment of these gums in food and other industries is a hazard for the sensitive individual from ingestion, inhalation, and surface contact of these gums.

5. Substitution of other gums for tragacanth, karaya, and arabic, and of synthetic mucilages and celluloses will help in offsetting the danger of sensitization encountered from their use.

REFERENCES

1. Speilman, A. D., and Baldwin, H. S.: Atopy to Acacia (Gum Arabic), J. A. M. A. **101**: 444, 1933.
2. Bullen, S. S.: Perennial Hay Fever From Indian Gum (Karaya Gum), J. ALLERGY **5**: 484, 1934.

3. Feinberg, S. M.: Karaya Gum Asthma, J. A. M. A. **105:** 505, 1935.
4. Bowen, R.: Karaya Gum as a Cause of Urticaria, Arch. Dermat. & Syph. **39:** 506, 1939.
5. Feinberg, S. M., and Schoenkerman, B. B.: Karaya and Related Gums as Causes of Atopy, Wisconsin M. J. **39:** 734, 1940.
6. Bohner, C. B., Sheldon, J. M., and Trenis, J. W.: Sensitivity to Gum Acacia, With a Report of Ten Cases of Asthma in Printers, J. ALLERGY **12:** 290, 1941.
7. Studdeford, W. E.: Severe and Fatal Reactions Following the Intravenous Use of Gum Acacia Glucose Infusion, Surg., Gynec. & Obst. **64:** 772, 1937.
8. Ivy, A. C., and Isaacs, B. L.: Karaya Gum as a Mechanical Laxative: An Experimental Study on Animals and Man, Am. J. Digest. Dis. **5:** 315, 1938.
9. Figley, K. D.: Karaya Gum Sensitivity, J. A. M. A. **114:** 747, 1940.
10. Brown, E. B., and Crepea, S. B.: Allergy (Asthma) to Ingested Gum Tragacanth, J. ALLERGY **18:** 214, 1947.
11. Gelfand, H. H.: The Allergenic Properties of the Vegetable Gums, J. ALLERGY **14:** 203, 1943.
12. Pacini, A. J.: Universal Colloid Company, New York. Personal communication.
13. Editorial: Colloid Laxatives, J. A. M. A. **127:** 992, 1945.
14. Pacini, A. J.: Quoting "Food Manufacturing," Blumenthal Chemical Publishing Company "Food and Food Products," Jacobs Interscience Publishers, and personal communications with specific manufacturing companies.

DISCUSSION

STEARNS S. BULLEN, SR., Rochester, N. Y.—Allergic reactions following exposure to vegetable gums are not very frequent, but when they do occur they are likely to produce severe and explosive symptoms.

It is known that the vegetable gums produce symptoms in susceptible people by contact and by inhalation. Dr. Gelfand has given further evidence that the ingestion of these gums may result in allergic reactions.

His case reports illustrate very well the fact that an ingested substance may produce reactions not only in the gastrointestinal tract but also on the skin and the mucous membrane of the respiratory tract and further that reactions may occur in the respiratory tract without any symptoms referable to the gastrointestinal tract. Also in one of his cases, although there was a four plus reaction on skin testing, no symptoms occurred on exposure to the gum. While all these phenomena are well known, it is seldom that they are so well illustrated in a small group of cases.

The constitutional reaction occurring on skin testing in one case which was intentionally reproduced should serve as a warning that skin testing with these vegetable gums is not without danger and should be done with the same care as with extracts of fish, cottonseed, and so forth.

Dr. Gelfand's list of substances in which these vegetable gums are used on a commercial scale will be of great aid to the clinician.

VITAL CAPACITY STUDIES TO DIFFERENTIATE TYPES OF BRONCHIAL ASTHMA*†

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THE technique of studying vital capacities was first introduced in the middle of the nineteenth century. In 1846 Hutchinson[1] who first used the term reported the vital capacity measurements in pulmonary conditions, based on 3,000 observations. Plesch[9] in 1913 studied the vital capacities of 4 patients with asthma. In the past thirty-five years many reports have appeared in the literature describing the diminution of vital capacities during attacks of bronchial asthma.[2-10]

The present study was carried out on a group of 130 patients with bronchial asthma from the services of St. Mary's and Waterbury Hospitals and from the private practice of the author. Patients with complications, such as cardiac disease and definite bronchiectasis, were excluded. The patients were studied for a period varying between four months and ten years. In each case a careful history was taken; this included present illness, past history, family history, and environmental history. Each patient was given a complete physical examination with special emphasis on the nose, throat, heart, and lungs; in addition, he received fluoroscopic studies. Some patients had roentgenographic examinations, and many had nasal smears examined for eosinophiles. In all cases, complete skin testing was done by the author by the intradermal method. The testing materials consisted of approximately 150 different foods, pollens, and other inhalants.

The patients were divided into two groups. Group A, the extrinsic, nonbacterial or immunologic type, included patients who gave positive skin reactions. The etiology was primarily not bacterial or infectious. An occasional attack might be induced by an upper respiratory infection but that was not the usual trigger mechanism. Group B, the intrinsic group, bacterial or nonimmunologic, consisted of patients who gave insignificant reactions on skin testing. The asthmatic attacks in the latter cases had no relation to seasonal pollens, other inhalants, or foods. As a rule the attacks were more severe during the day than at night. The patients were more uncomfortable during damp or cold days. Upper respiratory infections usually precipitated the attacks of asthma.

TECHNIQUE

A bell-type vitalometer was used for these studies; the bell floated in water and was connected by a chain and pulleys to a marker which recorded the respiratory excursion in cubic centimeters on a carbon paper. The patient stood in front of the spirometer, took the deepest possible breath, placed his

*From the Allergy Services of St. Mary's and Waterbury Hospitals.

†Read before the Fifth Annual Meeting of the American Academy of Allergy, Atlantic City, N. J., Dec. 6-8, 1948.

lips around a glass mouthpiece attached to the instrument, and blew all the air out of his lungs. This was usually repeated twice and the maximum reading obtained was taken as the vital capacity.

To obtain the patient's normal vital capacity the following procedure was carried out. The surface area was calculated from the height and weight of the patient without shoes or clothing by means of the formula of Dubois.[8] In order to calculate the vital capacity in liters, the square-meter surface area was multiplied by 2.5 for males and by 1.9 for females. A 15 per cent allowance recommended by Dreyer[10] for sedentary workers was the standard normal in this series.

ANALYSIS OF THE TABLES

In Table I we note that 72 per cent of all patients in Group A had a normal vital capacity between attacks and that 87 per cent had a vital capacity diminished less than 10 per cent. In Group B, we found no patient with a normal vital capacity in a relatively asthma-free period and only 5 per cent with a vital capacity diminished less than 10 per cent. In Group A, we found only 3 per cent with a vital capacity diminished more than 20 per cent, and no patient with a vital capacity diminished more than 30 per cent. On the other hand, in Group B 76 per cent of the patients had a vital capacity diminished more than 20 per cent, and 52 per cent of the patients had a vital capacity diminished more than 30 per cent. These figures reveal that permanent changes occurred in the vital capacities of the infectious asthmatics to a greater extent than in the noninfectious asthmatics.

TABLE I. PER CENT DIMINUTION IN VITAL CAPACITY IN PATIENTS WITH BRONCHIAL ASTHMA IN RELATION TO AGE

Group A

AGE IN YEARS	NORMAL	−10%	−20%	−30%	−40%	MORE	TOTAL
10 to 20	16	2	1	0	0	0	19
20 to 30	22	2	0	0	0	0	24
30 to 40	18	5	3	1	0	0	27
40 to 50	17	4	3	1	0	0	25
50 to 60	1	2	1	1	0	0	5
60 to 70	2	1	1	0	0	0	4
Total	76	16	9	3	0	0	104 Pts.
Percentage	72	15	10	3	0	0	100%

Group B

AGE IN YEARS	NORMAL	−10%	−20%	−30%	−40%	MORE	TOTAL
10 to 20	0	0	0	0	0	0	0
20 to 30	0	0	0	0	0	0	0
30 to 40	0	0	0	0	0	0	0
40 to 50	0	0	2	5	0	1	8
50 to 60	0	1	3	1	2	5	12
60 to 70	0	0	0	0	4	2	6
Total	0	1	5	6	6	8	26 Pts.
Percentage	0	5	19	24	24	28	100%

Since it was noted that the patients in Group A were younger at the time of examination than those in Group B, the next study was made using only those patients in Group A who were over 40 years of age (Table II). This

study revealed that 59 per cent of Group A in the older age period had a normal vital capacity, and that 80 per cent had a vital capacity diminished less than 10 per cent. In contrast, Group B, where all patients were over 40 years of age, only 5 per cent of the individuals had a vital capacity diminished less than 10 per cent. No patient in Group A over 40 years of age had a vital capacity diminished more than 30 per cent, whereas 52 per cent of Group B showed this degree of permanent alteration. It is obvious from these facts that age does not account for the difference in respiratory reserve found in the two types of asthma.

TABLE II. PER CENT DIMINUTION IN VITAL CAPACITY IN PATIENTS WITH BRONCHIAL ASTHMA BETWEEN 40 AND 70 YEARS OF AGE

Group A							
AGE IN YEARS	NORMAL	−10%	−20%	−30%	−40%	MORE	TOTAL
40 to 70	20	7	5	2	0	0	34 Pts.
Percentage	59	21	14	6	0	0	100%
Group B							
AGE IN YEARS	NORMAL	−10%	−20%	−30%	−40%	MORE	TOTAL
40 to 70	0	1	5	6	6	8	26 Pts.
Percentage	0	5	19	24	24	28	100%

In Table III a comparison of the two groups was made from the standpoint of the duration of the disease. Thirty-nine of the forty-two patients or 90 per cent of the patients in Group A who had had asthma no more than five years had 10 per cent or less reduction in vital capacity. Seventy-seven per cent of those with a duration of symptoms for more than twenty years had

TABLE III. PER CENT DIMINUTION IN VITAL CAPACITY IN PATIENTS WITH BRONCHIAL ASTHMA IN RELATION TO DURATION OF SYMPTOMS

Group A							
DURATION IN YEARS	NORMAL	−10%	−20%	−30%	−40%	MORE	TOTAL
Under 1 year	10	3	3	0	0	0	16
1 to 2	9	2	1	0	0	0	12
2 to 5	11	4	0	0	0	0	15
5 to 10	19	3	1	0	0	0	23
10 to 20	15	3	2	1	0	0	21
20 plus	12	1	2	2	0	0	17
Total patients	76	16	9	3	0	0	104
Percentage	72	15	10	3	0	0	100%
Group B							
DURATION IN YEARS	NORMAL	−10%	−20%	−30%	−40%	MORE	TOTAL
Under 1 year	0	1	0	0	0	0	1
1 to 2	0	0	0	0	1	1	2
2 to 5	0	0	2	1	1	2	6
5 to 10	0	0	1	1	1	3	6
10 to 20	0	0	1	2	1	1	5
20 plus	0	0	1	2	2	1	6
Total patients	0	1	5	6	6	8	26
Percentage	0	5	19	24	24	28	100%

vital capacities reduced less than 10 per cent. In Group B, only 11 per cent of the patients with asthma from one to five years had a vital capacity diminished less than 10 per cent, whereas no one with symptoms for more than twenty years had a vital capacity diminished less than 10 per cent.

Table IV compared the vital capacities in the two groups from the standpoint of sex. The female patients show a slightly greater tendency toward normal than the male patients. The difference however was negligible and may be discounted.

DISCUSSION

It is important to note the marked difference in the reduction in vital capacities between the two groups of patients. Whereas this may not necessarily indicate another criterion in differentiating the two types of asthma, it does give presumptive evidence that when the vital capacity is markedly diminished in the quiescent stage, one is dealing with an infectious or intrinsic asthma. We find that practically all of the patients in Group A show a return of vital capacity to approximately normal after the acute episode.

This may be explained by the fact that in extrinsic asthma the individual attacks are of relatively short duration. Between attacks the patient is generally symptom-free, which removes any permanent or continuous strain from the cardiorespiratory system. In contrast, the picture of intrinsic asthma differs. The severe attacks are of longer duration. During the relatively quiescent periods, the patient has mild symptoms, exacerbated by exercise or excitement. The pulmonary tissue never has an opportunity to recover its normal state. Irreversible changes such as emphysema and fibrosis take place which permanently reduce the respiratory reserve.

TABLE IV

Group A

PER CENT DIMINUTION IN VITAL CAPACITY IN PATIENTS WITH BRONCHIAL ASTHMA IN RELATION TO SEX

MALE							FEMALE						
NORMAL	−10 %	−20 %	−30 %	−40 %	MORE	TOTAL	NORMAL	−10 %	−20 %	−30 %	−40 %	MORE	TOTAL
42	12	7	1	0	0	62 Pts.	34	4	2	2	0	0	42 Pts.
68%	20%	10%	2%	0	0	100%	81%	9%	5%	5%	0	0	100%
88%							90%						

Group B

PER CENT DIMINUTION IN VITAL CAPACITY IN PATIENTS WITH BRONCHIAL ASTHMA IN RELATION TO SEX

MALE							FEMALE						
NORMAL	−10 %	−20 %	−30 %	−40 %	MORE	TOTAL	NORMAL	−10 %	−20 %	−30 %	−40 %	MORE	TOTAL
0	0	3	3	5	4	15 Pts.	0	1	2	2	2	3	11
0	0	20%	20%	33%	27%	100%	0	10%	18%	18%	27%	27%	100%

In order to compare patients of similar ages, Group A was further subdivided and a comparison was made of the individuals in this group who were over 40 years of age with the entire Group B, where all patients were over 40

years. A marked difference in respiratory reserve was still evident, which proved that the age differential found in Table I was not the cause.

Family history of atopy was found to be relatively high. Seventy-six per cent of the patients in Group A and 54 per cent in Group B gave a positive family history. The difference might possibly be explained in part by the fact that with older patients, as in Group B, it is more difficult to obtain accurate information regarding forebears.

The duration of the symptoms affected the vital capacities adversely in both groups, but the effect was less pronounced in Group A than in Group B. A marked alteration in vital capacity was present in the latter group regardless of the duration of symptoms, whereas patients in Group A usually had minimal reduction in respiratory reserve after many years of recognized periodically severe asthma.

In conclusion, this study indicates that the use of the vitalometer is another test in the armamentarium of the physician that may be used to aid him in differentiating between the two types of asthma.

SUMMARY

1. Patients with uncomplicated asthma were divided into two groups: Group A—the extrinsic, nonbacterial, or immunologic. Group B—the intrinsic, bacterial, or nonimmunologic.

2. Vital capacity studies revealed definite differences. Those of patients in Group A showed a much greater tendency to return to normal between acute attacks of asthma than those in Group B.

3. A comparison of patients of the same age revealed a much greater diminution in the vital capacities of Group B.

4. The duration of the symptoms affected both groups adversely.

5. Sex had no significant influence on vital capacity.

6. Vital capacity studies may give presumptive evidence in differentiating the two types of asthma.

REFERENCES

1. Hutchinson, John: On the Capacity of the Lungs and on the Respiratory Function, Etc., Lancet **1**: 630, 1846.
2. Lewis, W. H.: Pulmonary Ventilation in Bronchial Asthma, Ztschr. f. d. ges. exper. Med. **82**: 71, 1932.
3. Mudd, S. G.: Clinical Spirography; Observations in Bronchial Asthma, Boston M. & S. J.: **193**: 345, 1925.
4. Meyers, J. A.: Vital Capacity of the Lungs, Baltimore, 1925, Williams & Wilkins Company.
5. Meyers, J. A., and Cady, L. H.: Vital Capacity in 347 Cases of Disease of Bronchi, Lancet **45**: 66, 1925.
6. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration, Arch. Int. Med. **20**: 442, 1917.
7. Pescher, J.: Diminution in the Vital Respiratory Capacity in Chronic Bronchitis, Emphysema, and Asthma, Bull. Acad de méd., Paris **104**: 53, 1930.
8. Dubois, D., and Dubois, E.: Clinical Calorimetry: A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known, Arch. Int. Med. **17**: 863, 1916.
9. Plesch, J.: Die pathologische Physiologie des Lungenvolumes und seine Beziehung zum Krieslauf. Ztschr. f. Exper. Path. u. Therap. **13**: 165, 1913.
10. Dreyer, Georges: Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2**: 227, 1919.

DISCUSSION

DR. GEORGE I. BLUMSTEIN, Philadelphia, Pa.—Dr. Jennes has demonstrated a significant reduction in vital capacity in a group of patients with so-called intrinsic asthma as compared to a similar but much larger group with extrinsic asthma. This reduction bore no relationship to age at time of examination, or sex, but seemed to be proportional to the duration and severity of symptoms regardless of cause. Since vital capacity determination measures external respiration only, the indices obtained are only crude estimations of pulmonary efficiency. Alterations in pulmonary function as judged by the vital capacity during the course of bronchial asthma may be irreversible or reversible. The former are due to permanent changes in the lung parenchyma, the result of emphysema and fibrosis, while the latter are invariably due to bronchoconstriction and may be partially relieved by the administration of bronchodilator drugs. This study suggests that alterations in pulmonary parenchyma resulting in lowered vital capacity might aid in differentiating the nature of the underlying asthma. It would be untenable to use the vital capacity to classify the types of bronchial asthma since it measures changes in external respiration from any cause. Such lowered vital capacity could occur in any type of prolonged and severe asthma. One should associate, therefore, the alterations in the vital capacity with those found in the pulmonary tissues and not with the etiologic factors responsible for the asthma.

It has been amply demonstrated by Kaltreider, Cournand, and others that the residual air is markedly increased during the course of an acute asthmatic attack. The author's text is not clear regarding the clinical status of the subjects at the time of vital capacity determinations. Were they asymptomatic or was epinephrine administered routinely to those with residual symptoms? The presence of residual symptoms, subjective or objective, could have a profound effect on the vital capacity. Furthermore, the administration of epinephrine would only partially relieve this situation since a further increase in vital capacity could be obtained during a symptom-free state.

One is also struck by the marked preponderance of subjects in the extrinsic group. One might expect to find a higher percentage of the total group belonging to the intrinsic group. This is said advisedly since it is recognized that both factors may and often do exist in the same patient. The etiological factors in bronchial asthma may be likened unto a jig-saw puzzle, consisting of many parts, some large, some small, but all having a definite bearing on the final picture.

AN EVALUATION OF RADIUM TREATMENT TO THE NASOPHARYNX IN ASTHMATIC CHILDREN*

VICTOR L. COHEN, M.D., AND WILBUR J. FISHER, M.D.,† BUFFALO, N. Y.

THIS study was undertaken because of the favorable response obtained in asthmatic children after radium therapy to the nasopharynx as reported by Gay,[1] Ward, Levingston, and Moffatt,[2] and Crowe and Walzl.[3] The departments of Otolaryngology, Radiology, Pediatrics, and Allergy of the Children's Hospital of Buffalo were coordinated in order to evaluate this method of treatment.

A somewhat unique method of scoring at each visit was decided upon. This method was devised because of the difficulty in determining the severity and the amount of asthmatic symptoms a child may suffer when reported by the patient or his parent. The method of rating was devised on the basis of the following observations: (a) The amount and type of antiasthmatic medication a child required to overcome his symptoms. (b) The number of days of asthma reported by the child's parents and himself. (c) The number of days the child was in the hospital because of asthma. (d) The presence of sibilant and sonorous râles on auscultation of the chest when the child reported to the clinic.

It is obvious that some of these items portend a severer grade of asthmatic symptoms than others, and therefore, more points were allotted to those which indicate the more serious attack. Scoring for this study, therefore, was as follows: 1 point for each teaspoonful, capsule, or tablet of antiasthmatic medication; 3 points for each aminophyllin suppository taken; 5 points for each injection of Adrenalin or intravenous aminophyllin received; 5 points for each day the patient was hospitalized because of asthma; 1 point for each day of asthma reported by parents, and 5 points for sibilant and sonorous râles heard in the chest on auscultation when seen at the clinic. Sufficient medication was supplied by the clinic so that the symptoms could be adequately treated. The parents were instructed to give this medication only as needed. It may be supposed that some of these children may have been overly medicated, and, therefore, the use of this item is not a valid method of scoring. However, when the difficulty encountered in administering medication to most children is considered, it will be seen that this danger is quite remote, and we have found this to be the case.

Previous to radium therapy to the nasopharynx, the following studies were completed: (1) History, physical examination, special examination of the nasopharynx; (2) x-ray of the chest and sinuses, including determination roentgenographically of the amount of adenoid tissue in the nasopharynx; (3) nasopharyngeal cultures, nasal smears for percentage of eosinophiles present, com-

*Read at the Fifth Annual Meeting of the American Academy of Allergy, Atlantic City, N. J., Dec. 6-8, 1948.

†From the Children's Hospital, Buffalo, N. Y.

plete blood count, sedimentation rate; (4) skin testing by the intradermal method, in both weak and more concentrated dilutions; (5) no specific therapy was given after radiation was started, or during the period of study.

The actual radium treatment consisted of 6½ minutes of exposure to 100 milligrams of radium contained in the Crowe applicator applied to the nasopharynx in the recommended manner. Four such treatments were given, the interval between treatments being 21 days.

Patients were examined and interrogated in regard to their status, and medication was prescribed at approximate intervals of every other week. Information for scoring was obtained at each visit. In our charts, the score was divided by the number of weeks in the interval between visits and then recorded.

The scores were arranged according to the weeks subsequent to the completion of the radiation therapy, totaled, and averaged for a study of the effect on the entire group. In the case of special studies, the group was appropriately divided, totaled, and averaged in the same manner. Graphs were made of these charts; the horizontal line representing the weeks subsequent to radium therapy, and the vertical, the average score. In this way, it was felt that the amount and intensity of the asthmatic symptoms could be represented, relative to the weeks subsequent to radium therapy to the nasopharynx.

Fifteen cases were found acceptable for this study. All were children whose ages ranged from 4 to 16 years, the average age being 8.5 years. All these children were classified as perennial asthmatics. Each had positive skin reactions to various allergens. All except two had had tonsillectomy from 6 months to 9 years previous to this study. Some of these patients had been specifically desensitized for varying periods of time in our allergy clinic while others were new cases. The entire length of study was 34 weeks. A complete follow-up could not be accomplished in all cases. The shortest follow-up was 8 weeks, and the average of all follow-ups was 27.2 weeks.

RESULTS

1. *Total of all cases* (Fig. 1):

The average intensity of the asthma as demonstrated by our method was of 8.86 points. The trend of the graph indicated that improvement over the average intensity of asthma was obtained for the first 9 weeks. From the ninth to the sixteenth week the average was maintained, and after the twenty-sixth week, the intensity of asthma exceeded the average.

2. *Comparative study of patients with high sedimentation rates previous to radium therapy with those with normal sedimentation rates* (Fig. 2):

This study was done to determine if asthmatic children who showed signs of infection as demonstrated by the sedimentation rate obtained better results than those who had no signs of infection. The sedimentation rate was chosen for this purpose as it was considered to be the most sensitive and most persistent indication of infection available. In 3 patients, sedimentation rates were not done previous to treatment. Of the remaining children, it was found that 6 had normal sedimentation rates, and 6 had elevated rates (exceeding 10 mm.

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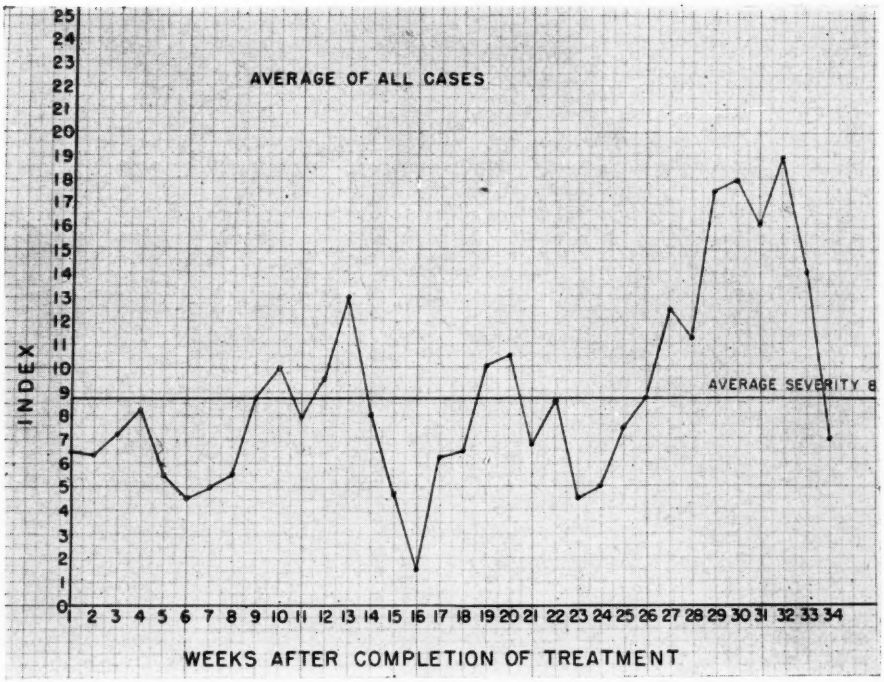
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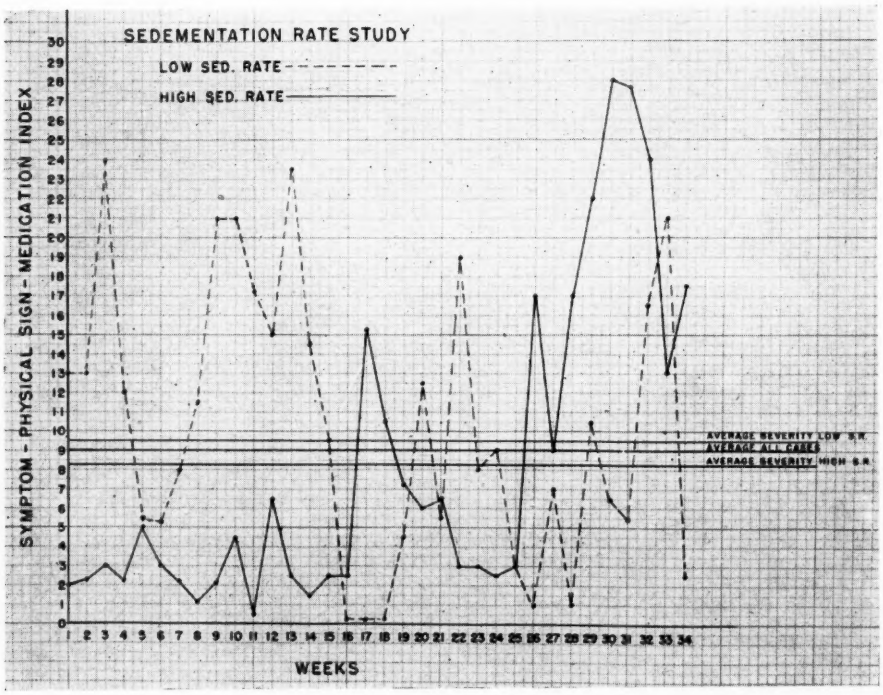
INDEX
AVERAGE SEVERITY 8
WEEKS AFTER COMPLETION OF TREATMENT

Fig. 1.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AVERAGE SEVERITY LOW S.R.
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AVERAGE SEVERITY HIGH S.R.
WEEKS

Fig. 2.

per hour by Wintrobe method). The graph indicates that patients with high sedimentation rates who received radium treatment to the nasopharynx obtained better results from this treatment than those with normal sedimentation rates. Improvement in these patients was obtained until the twenty-sixth week, whereas no notable change can be observed in those with normal sedimentation rates. This would suggest that patients harboring infection obtain better results from this type of treatment.

3. *Adenoid tissue study:*

The amount of adenoid tissue in the nasopharynx of each patient was estimated* from a lateral x-ray plate of the nasopharynx. The patients were thus classified from 0 to 4 plus. Patients having 3 and 4 plus amounts of adenoid tissue were compared to those having 0 to 2 plus amounts, totaled, and graphed. Eight patients had 3 or 4 plus adenoids, 7 had 0 to 2 plus.

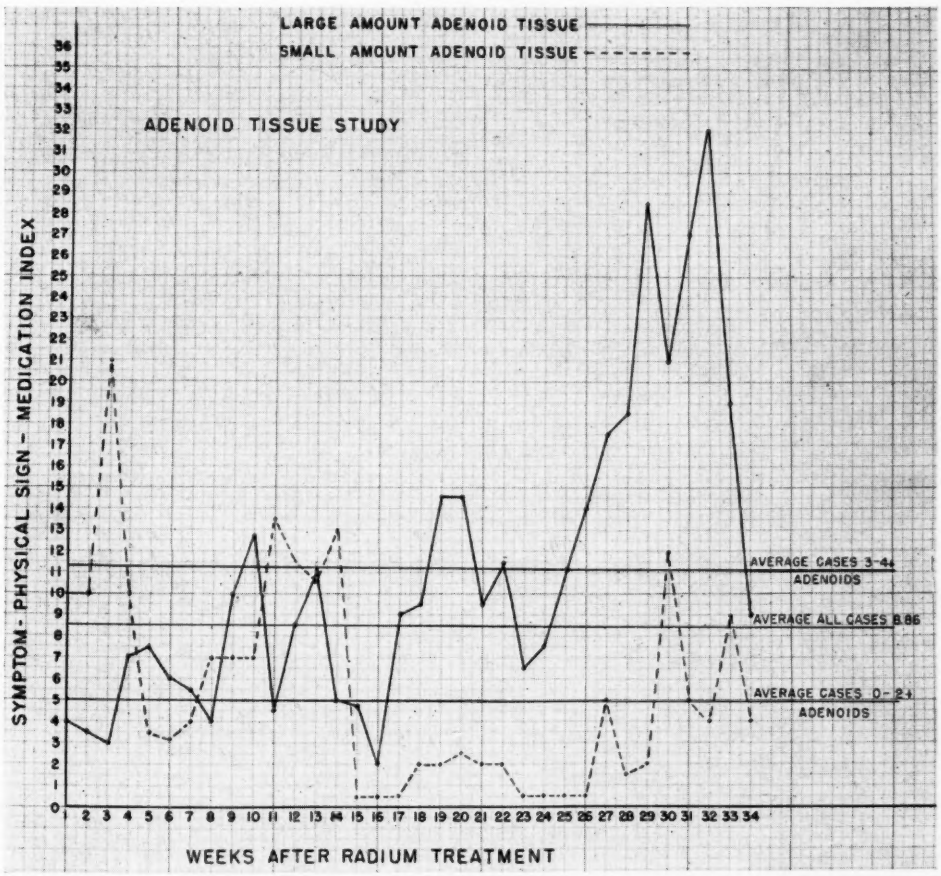

LARGE AMOUNT ADENOID TISSUE
SMALL AMOUNT ADENOID TISSUE
ADENOID TISSUE STUDY
SYMPTOM - PHYSICAL SIGN - MEDICATION INDEX
AVERAGE CASES 3-4+ ADENOIDS
AVERAGE ALL CASES 8.86
AVERAGE CASES 0-2+ ADENOIDS
WEEKS AFTER RADIUM TREATMENT

Fig. 3.

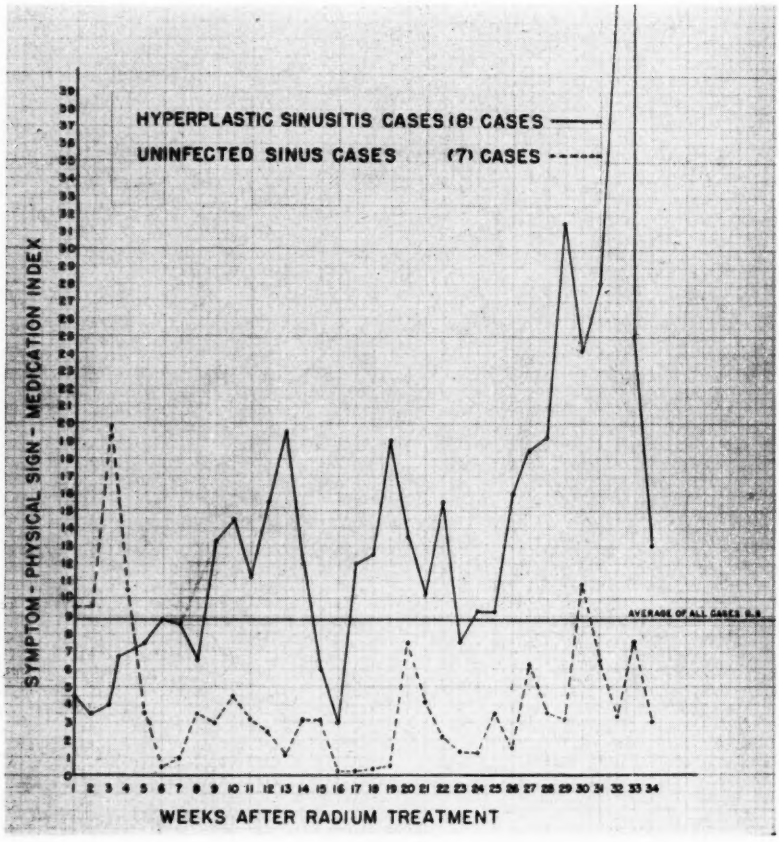
Fig. 3 indicates that although the response in the group with the smaller amount of adenoid tissue was not as prompt initially as in those with a greater

*Acknowledgment is made by the authors to Dr. G. Newton Scatchard, Chief of Radiology, Children's Hospital, and Assistant Professor of Radiology, University of Buffalo, for his help with this portion of the study.

amount of tissue, it was much more sustained. Also patients having had smaller amounts of adenoid tissue previous to radium therapy obtained, in general, a better result from the treatment than those having greater amounts of tissue previous to radium therapy.

4. *Sinus study* (Fig. 4):

Patients having hyperplastic sinusitis, as demonstrated roentgenographically previous to treatment, were compared with those having no sinus involvement. It was found that 8 patients had one or more demonstrably involved sinuses while 7 had no sinus involvement. Fig. 4 shows that patients with normal sinuses obtained a better result from treatment than those showing hyperplastic sinusitis, although initially the response was not as rapid. The hyperplastic sinusitis patients showed a more rapid improvement, but returned to above-average status 8 weeks after treatment and remained above average for the remainder of the study.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SYMPTOM - PHYSICAL SIGN - MEDICATION INDEX
AVERAGE OF ALL CASES
WEEKS AFTER RADIUM TREATMENT

Fig. 4.

DISCUSSION

On consideration of the information obtained from our method of studying these cases, certain impressions are suggested. The beneficial response obtained directly following the course of radium therapy as demonstrated by the graph

of the entire group (Fig. 1) is very similar to the results obtained in cases treated by nonspecific therapy. However, the better response to radium therapy in patients with a high sedimentation rate as compared with those with a normal sedimentation rate (Fig. 2) would tend to indicate that infection in the nasopharynx is benefited by this treatment. The observation that patients having least adenoid tissue in the nasopharynx previous to radium therapy obtained the better results (Fig. 3) would again suggest that penetration of these radiations into infected tissue is an important factor in the mode of action of this therapeutic measure. One must keep in mind, however, the possibility that hypertrophy of the lymphoid tissue may be merely another manifestation of severe asthma, and that radium therapy may have little to do with the less severe asthma in patients having little adenoid tissue in the nasopharynx.

Whether hyperplastic sinusitis in asthmatic patients is the cause or result of the asthmatic process is still a controversial subject. Whatever the status of the involved sinuses may be in regard to the allergic process, our study definitely demonstrates the increased severity of symptoms in patients having hyperplastic sinusitis. Radium treatment of the nasopharynx obviously is less effective in patients having hyperplastic sinusitis than in patients having uninvolved sinuses as demonstrated by our studies.

SUMMARY

1. Radium treatment of the nasopharynx in our experience cannot be considered to be a panacea for any type of asthma, but as revealed in this study must be considered as an auxiliary to other forms of treatment.

2. Improvement in asthmatic symptoms may be expected for about 17 weeks following radium treatment to the nasopharynx in most cases.

3. Patients having a high sedimentation rate will in general obtain better results from radium therapy to the nasopharynx than those with normal sedimentation rates.

4. Patients having the least amount of adenoid tissue in the nasopharynx obtain more relief from asthma following radium therapy than those having a greater amount of adenoid tissue.

5. Patients with normal sinuses obtain better relief from asthma after radium therapy than patients with hyperplastic sinusitis.

6. Therefore, if radium treatment be considered for therapy of the asthmatic child, it would appear that better results may be anticipated in a case with an increased sedimentation rate, normal sinuses, and little or no adenoid tissue in the nasopharynx.

The authors gratefully acknowledge the help of Dr. Mitchell I. Rubin, Chief of Pediatric Service, Children's Hospital, and Professor of Pediatrics, University of Buffalo Medical School, for his efforts in organizing this study.

REFERENCES

1. Gay, Leslie N.: The Treatment of Residual Lymphoid Tissue in the Nasopharynx by Radium, J. ALLERGY **17**: 348, 1946.

2. Ward, Arthur T., Jr., Livingston, Samuel, and Moffat, D. A.: Asthma in Children, J. A. M. A. **133**: 15, 1947.
3. Crowe, S. J., and Walzl, E. M.: Irradiation of the Hyperplastic Lymphoid Tissue in the Nasopharynx, J. A. M. A. **134**: 2, 1947.

DISCUSSION

DR. FURSTENBURG, Baltimore, Md.—Dr. Cohen's paper brings into focus one of the problems that Baltimore allergists are facing in their day-to-day practice. His study raises the question of the irradiation of the nasopharynx for the treatment and prevention of asthma. Due to the observations of Crowe and his co-workers, papers concerning the benefits of radon to the nasopharynx routinely mention its benefits for selected cases of asthma and nasal allergy.

I have been reviewing the youngsters that have recently come to our office with symptoms and findings compatible with respiratory allergy with special interest in the incidence and effect of surgical procedures to the nasopharynx. My observations at this time concern 86 consecutive patients, 13 years of age or younger, with allergic rhinitis, hay fever, asthma, asthmatic bronchitis, and certain cases of rhinitis of undetermined origin. Of these 86 patients, 35 (40 per cent) had a series of radium treatment before coming to the office. Three patients had had two courses of the treatment.

In all 35 patients the radon had been applied after the allergic symptoms had begun and in no case did it fundamentally alter the course of the allergy or the nature of the allergic symptoms. Seventeen of the patients given radium had asthma or asthmatic bronchitis and none of these showed distinct improvement. In an occasional case when administered for a chronic, stuffy nose, there seems to be some temporary improvement. When radon was applied for recurrent otitis media or for deafness, our histories showed that it was often efficacious.

From the study of patients seen in our practice we would question whether irradiation of the nasopharynx is beneficial in respiratory allergy. Obviously we have only seen the failures of radon therapy, but from the data we have on hand, neither the asthmatic, nor the patient with allergic rhinitis, is helped by radium. Dr. Cohen is to be congratulated for presenting his study on this problem. It should help check the enthusiasm with which the otolaryngologists and the pediatricians advise the use of this procedure.

BRONCHOSCOPIC THERAPY IN ALLERGIC ASTHMA*

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BRONCHOSCOPY has been employed in bronchial asthma mainly for diagnostic purposes. Early advocates[1] of therapeutic bronchoscopy in allergic asthma observed that aspiration of the characteristic tenacious mucus benefits certain patients.

In 1938, I reported that bronchoscopy had been lifesaving in several instances.[2] It was then suggested that all asthmatic patients in a moribund state should be given the benefit of this treatment. Although an increasing number of clinicians[2] concur in this view, there is considerable reluctance on the part of both bronchoscopists and allergists to employ the procedure in an emergency. For this reason, the following review of the operative and postoperative records of 180 therapeutic bronchoscopies on 127 patients with allergic asthma was made with the view of setting up distinct criteria for the indication and contraindication of bronchoscopic therapy. Most of these patients had been in hospitals between two to five days and had been refractory to other therapeutic measures. A small number were hospitalized for the purpose of having the bronchoscopic treatment. These were performed by several bronchoscopists.

MECHANISM OF ASTHMA

Wheezing is effected by air passing through partially obstructed bronchi. This obstruction is caused by mucus which is present throughout the ramifications of the bronchial tree as well as by bronchospasm. From clinical experience it appears that the mucus becomes thicker in consistency and its expulsion the more difficult, the more protracted the condition. The expectorated material resembles that seen in hay fever in which, at the beginning of the season, the nasal and sinus mucosa secretes a copious, watery fluid, which in time becomes thicker and more purulent. Wheezing and cough are relieved when some of the mucus is expectorated; conversely, when elimination is interfered with the attacks become more severe. An unusual degree of dryness of the respiratory surfaces tends further to make the mucus sticky and adherent to the bronchial walls. In this state the bronchial dilation brought about by the action of epinephrine and Aminophyllin may no longer suffice or one may become "epinephrine-fast." The gluelike material behaves like a foreign body. It constitutes a check-valve to the portion of the lung distal to it, allowing the air to enter during inspiration, but trapping it during the expiratory phase of the respiration.

INDICATIONS

With this in mind, the principal reason for a therapeutic bronchoscopy in allergic asthma is to remove the thick, tenacious mucus which accumulates in the bronchial tree and interferes with respiration. Although only the larger

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portions of the bronchi can thus be cleared of mucus by aspiration, it is also likely that the distal portions benefit indirectly from this procedure. The dilating action of the lavaging fluid and the clearing of the upper passages may lead to spontaneous evacuation of the bronchioles after the withdrawal of the bronchoscope.

In this series of cases, bronchoscopy was employed in the following situations: (1) To prevent a moribund patient from becoming asphyxiated through accumulation of mucus; (2) To break up a chronic asthmatic state—regardless of its severity; (3) To remove a single mucous plug which, through complete obstruction of a bronchus, has produced partial or total pulmonary atelectasis; (4) To dilate strictures of the bronchi which follow inflammatory changes of the bronchial mucosa; (5) To remove mucous secretion from bronchiectatic areas.

1. *Emergency.*—Eight patients in this series of 127 (Table I) were in a moribund state. Either following sudden onset, or developing gradually, their condition had deteriorated in such a manner that it had become refractory to all medication. The expectoration, which had been free at first and had yielded copious and viscid material, had gradually "dried up" and become very laborious. In all but one patient (Case 1) the asthma subsided after between 30 to 60 c.c. of thick, pasty material had been removed through aspiration and lavage with saline solution.

TABLE I

	NUMBER OF CASES	NUMBER OF BRONCHOSCOPIES	RELIEF
Emergency	8	12	11
Chronic asthma	119	168	62
Including:			
Atelectasis	4	4	3
Bronchostricture	4	3*	3
Irreversible bronchiectasis	2	8	6
Total	127	180	73

*On one patient, dilatation not attempted.

In a 16-year-old girl, with extremely severe attacks of asthma appearing regularly before her menses, bronchoscopic treatment appeared to be lifesaving on four occasions. When, on admission to the hospital during another such attack, the bronchoscopist was not immediately available, the patient expired.

2. *Status Asthmaticus.*—By far the majority of bronchoscopies were carried out for the purpose of breaking up an intractable, not necessarily severe, state of asthma which did not yield to other modes of treatment. If the sputum of a chronic asthmatic presents bronchial casts, if each coughing spell results in severe wheezing which is somewhat relieved upon expectoration, or if there is evidence that "the mucus does not come up any more," bronchoscopic treatment should be considered. Upon endoscopic inspection, there is in addition to the obstructing mucus, narrowing of the bronchial lumen and collapse of the

posterior walls of the trachea and bronchi on expiration; the bronchial mucosa exhibits acutely inflamed areas which are interspersed with normal appearing ones. On 119 patients, 168 bronchoscopies were performed (Table I). In 9, a single bronchoscopic treatment was followed by complete relief from asthma, and 53 additional patients improved considerably following one or more bronchoscopic treatments; the remaining 57 experienced little or no benefit. Among the latter there were several individuals in whom the asthma was aggravated, or induced, by psychogenic factors. Here, bronchospasm may be so severe that it resembles a cicatricial stenosis and little or no mucus is found in the bronchi (Fig. 1).

When the mucus is not adequately removed through the bronchoscope, or expectorated subsequently, patients may relapse into the asthmatic state after initial improvement. In this case, it is advantageous not to wait longer than one or two days for a second bronchoscopic treatment in order to remove the mucus more thoroughly.

3. *Atelectasis.*—A single mucous plug may lead to either complete or partial atelectasis of a pulmonary lobe, according to whether a main or secondary bronchus is obstructed (Fig. 2). Because of the emphysema and wheezing in asthma, the physical findings of atelectasis are not as distinct as in nonasthmatic cases. Localized excessive wheezing about the atelectatic areas is of diagnostic significance. Complete atelectasis of a single pulmonary lobe is not an uncommon complication of allergic asthma. In 3 of these cases the bronchoscopist could withdraw the mucus and the lung promptly expanded. However, in one patient, a 3-year-old boy, the narrowness of the bronchus prevented the aspiration of the plug. The patient attempted to seek relief by moving to another climate.

4. *Stricture of Bronchi.*—Prickman and Moerch[3] first drew attention to this complication in asthma which presumably originates from inflammation of the bronchial mucosa. It is characterized by exceedingly chronic and persistent wheezing, nonproductive cough, suppression of breath sounds and fremitus over the affected area, and episodes of fever due to localized pneumonitis (Fig. 3). Here, too, wheezing around the affected areas is in excess of that heard in other parts of the lungs. Whereas Prickman's paper suggests a higher incidence of this condition, our series revealed only 4 cases in which bronchostrictures were demonstrated, 2 of which exhibited a tuberculous process associated with allergic asthma (Fig. 4). Three of the 4 patients showed complete and dramatic recovery of long-standing asthma following a single bronchoscopic dilatation. In the fourth patient the stricture was so extensive that dilatation of the bronchi was not attempted at bronchoscopy because of the danger of perforating the bronchus (Fig. 5).

5. *Bronchiectasis.*—Permanent bronchiectasis is probably a much less common complication of allergic asthma than the literature indicates. In every patient with protracted asthma one would expect some temporary widening of the terminal bronchi, because of the accumulation of thick mucus observed on bronchoscopy in the ramifications of the bronchial tree. Indeed, bronchograms on several patients indicate that such temporary bronchiectasis is no longer in

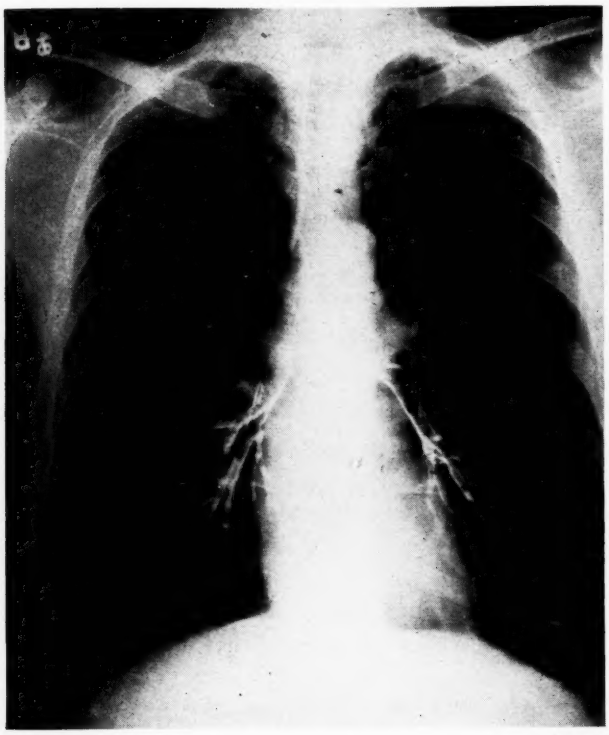

Fig. 1.—Bronchogram showing stoppage of Lipiodol in lower portions of lungs, probably as results of bronchospasm. Neither bronchoscopic lavage nor autopsy findings (three months later) revealed mucus in these areas.

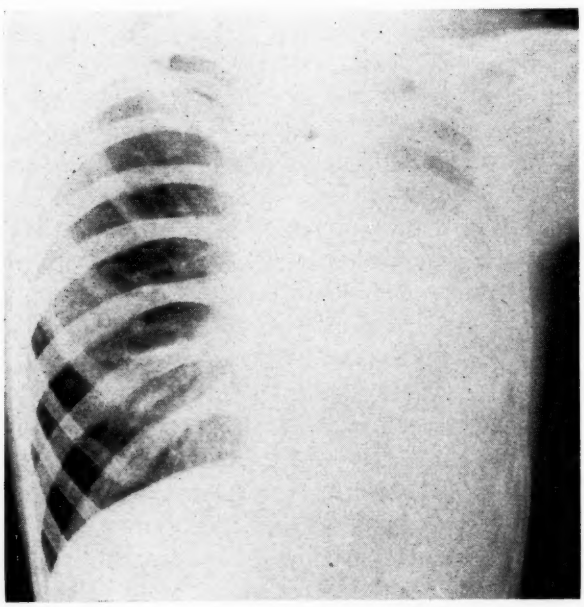

Fig. 2.—Roentgenogram of severe chronic asthma complicated by atelectasis of left lung.

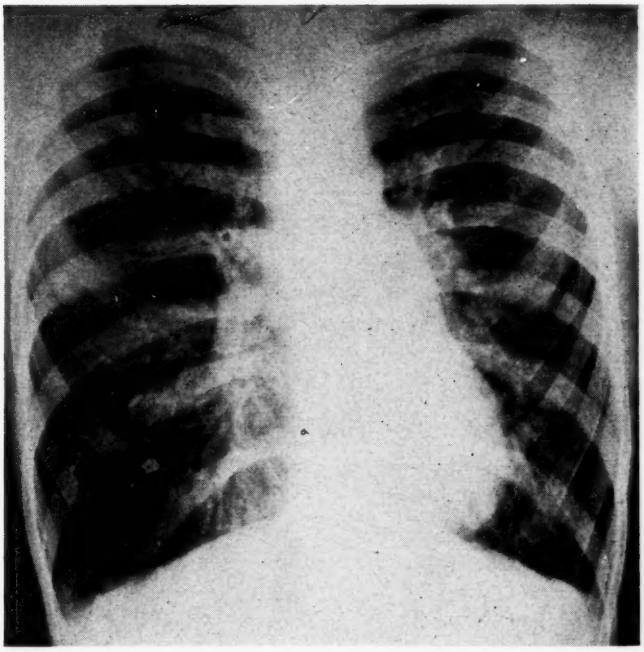

Fig. 3.—Roentgenogram of same patient as in Fig. 2. Prompt recovery after aspiration of a mucous plug.

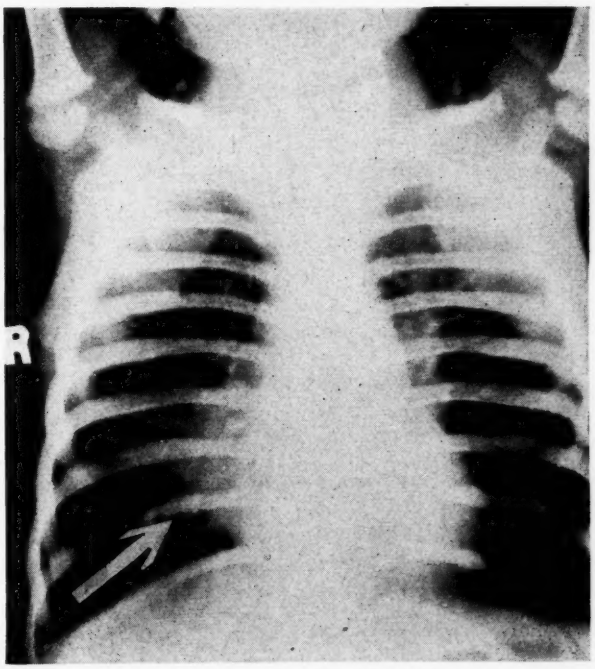

Fig. 4.—Roentgenogram of chronic pneumonitis following obstruction of a bronchus by mucus.

evidence after the attack has subsided (Fig. 6). Only 2 patients of this series had massive irreversible bronchiectasis of the type shown here. It is readily recognized on bronchoscopy, and responds favorably to bronchoscopic lavage. While these were allergic individuals, we are not prepared to state that the bronchiectasis was caused by asthma.

If bronchiectasis is confined to the small ramifications of the bronchial tree, bronchoscopic lavage is not as successful as in the more extensively widened bronchi. Bronchospasm may prevent the proper evacuation of the smaller bronchi.

If a bronchogram is desirable when bronchiectasis is suspected, it should be borne in mind that reactions are not uncommon and that exitus from this procedure has been reported.[4] Allergic patients may be sensitive to the contrast material. Furthermore, the "crowding" of oil into a bronchial tree, filled to capacity with mucus, may lead to asphyxiation.

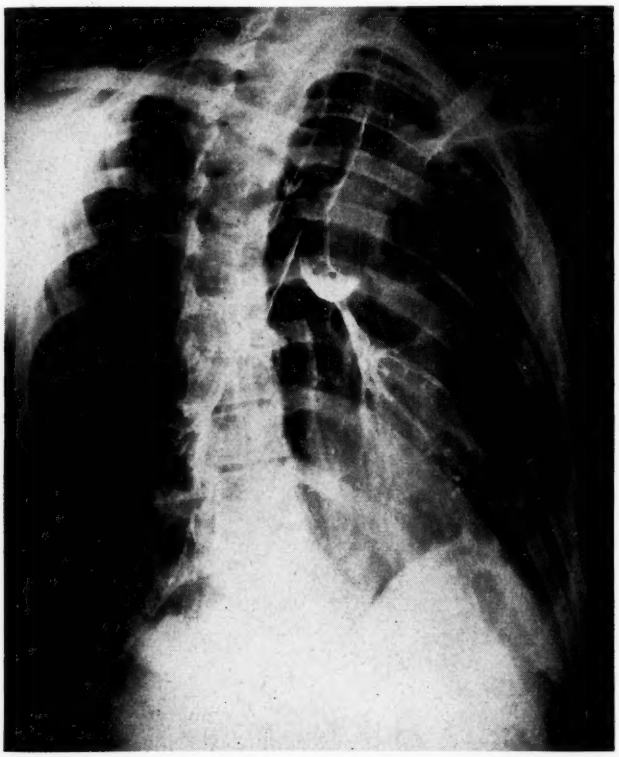

Fig. 5.—Bronchogram showing broncostenosis and bronchial diverticulum in tuberculosis associated with allergic asthma.

CONTRAINDICATIONS

Bronchoscopic treatment should not be employed where there is little or no mucous secretion or when the sputum is thin and watery. This is true: (1) in asthma of short duration where there is edema of the alveoli associated with, or followed by, pneumonitis[1, 5]; (2) in incipient asthma characterized by a non-productive pertussis-like bronchitis,[6] in which bronchoscopy reveals petechial

hemorrhages, and occasionally urticaria-like edema of the bronchial mucosa; (3) in sudden severe attacks (allergic shock) following injection, ingestion, or inhalation of antigens to which extreme sensitivity exists where bronchospasm dominates the clinical picture; and (4) in asthmatic attacks of psychosomatic origin.

HAZARDS FROM BRONCHOSCOPY

The reluctance of bronchoscopists to avail themselves of this procedure more frequently in allergic asthma can be understood because, in asthmatics, emergencies may arise from sensitivity to, and intolerance of, anesthetics and other drugs administered before and during the bronchoscopy.

1. *Anesthetics.*—On several occasions we encountered pharyngeal edema followed by dyspnea, immediately after application of cocain or Pantocain to the pharynx. If such signs of sensitivity to the anesthetic are recognized promptly, immediate administration of large doses of epinephrine, injected subcutaneously (0.5 to 1.0 c.c.) and applied locally, may avert disaster. Intolerance to local anesthetics, on the other hand, manifests itself through such

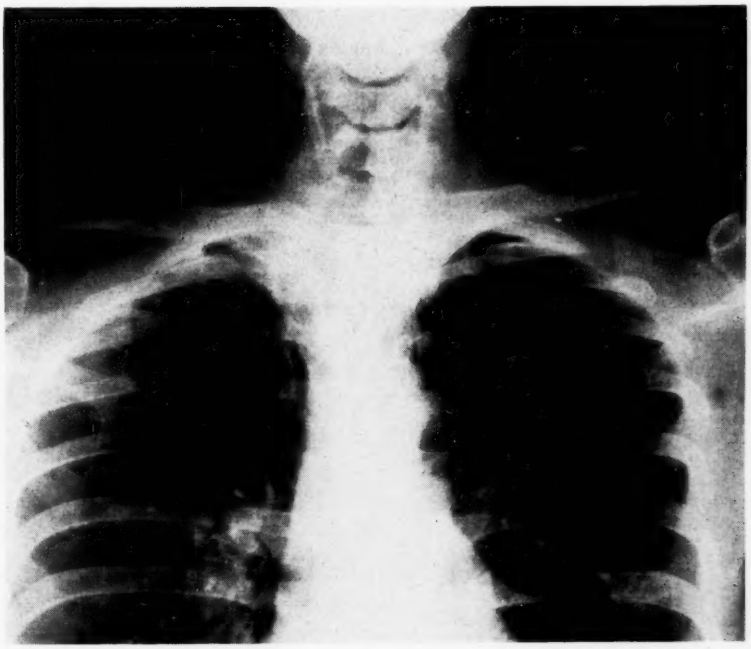

Fig. 6.—Roentgenogram of patient with allergic asthma associated with healed tuberculous scar. Bronchoscopy revealed a cicatricial stenosis of a large bronchus associated with atelectasis in right upper lope. Note deviation of trachea; sparsity of x-ray findings in contrast with marked pathology.

premonitory symptoms as flushing of the face, twitching of the muscles of the extremities, extreme nervousness, sensation of "heat" in abdomen, stertorous breathing, and, finally, convulsions.[7] Pentothal sodium, administered intravenously, is considered a potent antidote. This drug, incidentally, should not be employed as a general anesthetic for bronchoscopy. In a patient who received an intravenous injection of 5 per cent Pentothal Sodium, spasm of the

epiglottis developed which threatened asphyxiation. Under great difficulties the surgeon succeeded in prying open the epiglottis with the bronchoscope and introducing the instrument into the bronchus. Ether anesthesia is both impractical and not devoid of danger from sensitivity and intolerance.

2. *Preoperative Drugs.*—As to preoperative medication, allergic patients are particularly susceptible to hazards from opiates. Codeine, morphine, Dilaudid, and Demerol, have, in my experience, led to aggravation of asthma or to severe shock.

One-sixth grain of Pantopon, administered subcutaneously, caused one of our patients to develop marked cyanosis, Cheyne-Stokes respiration, and cardiovascular collapse within ten minutes. Two hours later an emergency bronchoscopy yielded only small amounts of thin mucous secretion; there was no bronchospasm; the bronchial mucosa exhibited evidence of inflammation throughout. The patient expired four hours later. The autopsy revealed marked edema and congestion in the liver, spleen, and brain, bilateral bronchiectasis, and pulmonary emphysema. Intolerance to Pantopon was considered the cause of death.

3. *Endoscopic Medication.*—Because of the danger of sensitization, we should refrain from endoscopic application to the bronchi of such drugs as cocain, Argyrol, Guaiacol, silver nitrate, 1 per cent Mercurochrome, or menthol, as originally advocated by Lukens and others.[1] We have also abandoned the instillation of sulfathiazole solution into the bronchi.

4. *Other Accidents.*—Severe dyspnea and unproductive cough may occur within a short period after the bronchoscopy. This indicates that some of the tenacious material had been freed, but is now blocking some of the bronchial passages. A fatality reported by Lell[1] might thus be explained. In this emergency, one should be prepared to reintroduce the bronchoscope promptly for another aspiration.

A rather unique accident was encountered during a bronchoscopy in a patient presenting a bronchostenosis. During the attempt to dilate the stenosed bronchus, the dilating bougie was locked so tightly by the spastic contraction that it broke off upon withdrawal. The object was later removed uneventfully by thoracotomy. Since this operation, the patient had been free from asthma.

Except for these noted instances there were no accidents in this series, a fact which may be attributed to the precautions outlined below, especially the more discriminate use or complete abandonment of anesthetics.

TECHNIQUE

The following is the technique employed in bronchoscopic lavage. As little anesthesia as possible is used. In cases with marked anoxemia, sufficient drowsiness is present to dispense with anesthesia altogether. If the preoperative administration of 1½ grains of phenobarbital does not suffice for adequate relaxation of the patient, a 2 per cent solution of Pantocain is applied to a small test area in the buccal mucosa. This area is observed for ten minutes. If there is no unusual degree of edema and hyperemia the anesthetic is applied to the pharyngeal wall. One-half of a 3¾ grain ampoule of Aminophyllin is then administered intravenously which may be followed by 5.0 c.c. (50 mg.) of

Benadryl intravenously and 0.1 c.c. of 1:1,000 epinephrine, subcutaneously if necessary for bronchial relaxation. The other half of the ampoule of Aminophylline is held in readiness for administration during the procedure should the bronchospasm remain excessive. Oxygen may be administered throughout the procedure. After inspection of the bronchi and aspiration of mucus, 10.0 c.c. of physiologic saline solution is injected through the bronchoscope and aspirated. Occasionally 0.2 c.c. of a 1:1,000 solution of epinephrine is admixed to the lavaging fluid if required by continued excessive spasm. Larger doses of epinephrine lead to unpleasant reactions from the pharmacological action of the drug.

The presence of inflammatory changes in the bronchial mucosa may call for introduction of penicillin solution (100,000 units in 20 c.c. of saline). For this reason, an effort is made before the bronchoscopy to determine by both history and intradermal test whether or not sensitivity to penicillin exists. In spite of the fact that previous administration of the antibiotic produced no ill effect, the possibility of sensitivity to the drug should be recognized. Even if no immediate ill effect ensues, penicillin may induce extremely severe asthma between five to eleven days after the bronchoscopy, associated with the serum sickness type of reaction from penicillin.

SUMMARY

In reviewing our over-all results with bronchoscopy, relief in 73 out of a total of 180 cases appears to be somewhat disappointing, especially considering that the asthmatic attacks may recur at a later date.

However, the saving of lives in this group and the breaking up of extremely chronic asthma in other individuals, renders bronchoscopic lavage one of our most important—if not the most important—therapeutic measures.

REFERENCES

1. *a.* Weille, F. L.: Bronchoscopy in Asthma, J. ALLERGY **2**: 206-207, 1932.
   b. Lukens, R. M.: Bronchoscopy in the Treatment of Asthma, Laryngoscope **35**: 227, 1936.
   c. Clerf, C. H.: Present Status of Bronchoscopy in Bronchial Asthma, Ann. Int. Med. **9**: 1050-1056, 1936.
   d. Tucker, G.: Bronchoscopy in Pulmonary Diseases, Ann. Int. Med. **8**: 444, 1934.
   e. Prickman, L. E., and Vinson, P. P.: Bronchoscopy in Asthma, J. ALLERGY **4**: 286-293, 1933.
   f. Van Loon, E. L., and Diamond, C.: Bronchoscopic Aspects of Asthma in Children, Am. J. Dis. Child. **63**: 217, 1942.
   g. Gompertz, J. L.: Bronchoscopy: Its Role in the Treatment of Asthma, California & West. Med. **58**: 10-11, 1943.
   h. Lell, W. A.: Bronchoscopy as an Aid in the Diagnosis and Treatment of Allergic Pulmonary Diseases, Arch. Otolaryng. **43**: 49-58, 1946.
2. *a.* Waldbott, G. L.: Emergency Treatment in Asthma (Asthmatic Crisis), J.A.M.A. **110**: 1423-1427, 1938.
   b. Bases, L., and Kurtin, A.: Prevention of Death in Status Asthmaticus, Value of Bronchoscopy, Arch. Otolaryng. **35**: 47, 1942.
   c. Clerf, L. H.: Progress in Bronchology, J.A.M.A. **136**: 733-736, 1948.
3. Prickman, L. E., and Moerch, M. S.: Bronchostenosis Complicating Allergic and Infectious Asthma, Ann. Int. Med. **14**: 387-392, 1940.
4. Mahone, G. S.: Reaction Following Bronchography with Iodized Oil, J.A.M.A. **130**: 194-196, 1946.
5. Waldbott, G. L.: Pathologic Changes in Asthmatic Infants, Amer. J. Dis. Child. **49**: 1531-1539, 1935.
6. Waldbott, G. L.: Allergic Bronchitis, J. Lab. & Clin. Med. **13**: 943, 1928.
7. Waldbott, G. L.: Asthma Due to a Local Anesthetic, J.A.M.A. **99**: 1942, 1932.

Original Articles

THE EFFECTS OF ANTIHISTAMINIC DRUGS UPON THE EXCRETION OF ASCORBIC ACID BY RATS*†‡

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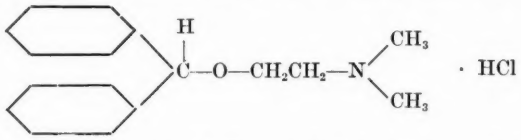
ASCORBIC acid has been shown by many investigators to be of importance in increasing the resistance of the body to toxic agents. It has been reported to be beneficial in the treatment of lead poisoning,[1] and to protect the body against the toxicity of a number of drugs.[2-5] It is also involved in the resistance of the body to infection.[6-9]

Longenecker and associates[10-12] have investigated the effects of a large number of substances upon the excretion of ascorbic acid by rats. They found that many compounds cause marked elevation in excretion, and that this is due to increased ascorbic acid synthesis. Presumably this production of ascorbic acid is a protective response of the body toward the toxic agents. Among the substances found to cause increased ascorbic acid synthesis were various terpenes, many barbiturates, antipyretics, paraldehyde, and Chloretone. Many of the effective substances were nerve depressants. In view of these facts, and because the antihistaminic drug Benadryl has a decided narcotic action, it and a number of the other antihistaminic drugs were investigated to determine their effects upon ascorbic acid synthesis in the rat.

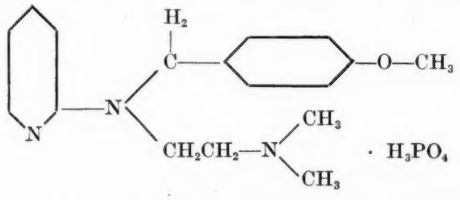
The general experimental plan was similar to that followed by Longenecker and associates. The antihistaminic compounds tested were Benadryl, Histadyl, Neo-Antergan, Thephorin, Pyribenzamine, Trimeton, and Antistine.

Benadryl: β-dimethylaminoethyl benzhydryl ether hydrochloride.*



*The drugs for this work were kindly supplied as follows: Benadryl, Parke, Davis & Company, Detroit, Mich.; Neo-Antergan, Merck and Company, Inc., Rahway, N. J.; Histadyl, Eli Lilly & Company, Indianapolis, Ind.; Thephorin, Hoffmann-La Roche, Inc., Nutley, N. J.; Pyribenzamine and Antistine, Ciba Pharmaceutical Products, Inc., Summit, N. J.; Trimeton, Schering Corporation, Bloomfield, N. J.

Neo-Antergan: N-α-pyridyl, N-p-methoxybenzyl-N′, N′-dimethyl-ethylenediamine phosphate.

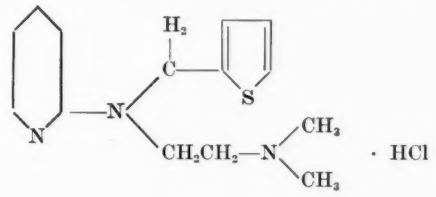


*From the Department of Biochemistry, University of Oregon Medical School.

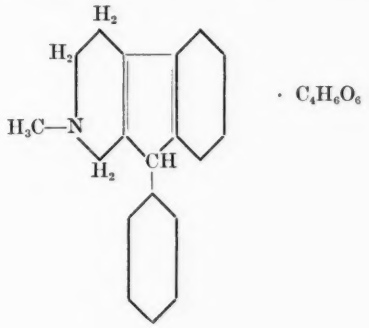
†The data in this paper were taken from a thesis presented by Ruth D. Peterson in partial fulfillment of the requirements for the degree of Master of Science, University of Oregon Medical School, 1948.

‡Aided by a grant from the Rinehart Foundation, Wheeler, Oregon.

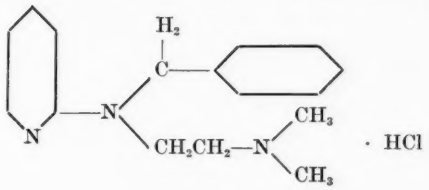
Histadyl: N-(α-pyridyl-N-(α-thienyl)-N′, N′-dimethylethylene-diamine hydrochloride.



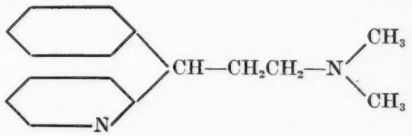
Thephorin: 2-methyl-9-phenyl, tetrahydro-1-pyridindine hydrogen tartrate.



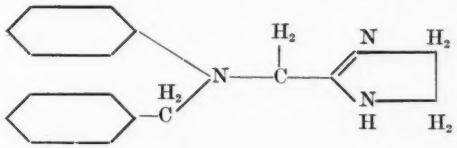
Pyribenzamine: N, N-dimethyl-N′-benzyl-N′-(α-pyridyl)-ethylene-diamine monohydrochloride.



Trimeton: Phenyl(α-pyridyl)(β-N, N-dimethylaminoethyl)methane.



Antistine: 2-(N-phenyl-N-benzyl-aminomethyl)imidazolin.



Six rats were included in each series. They were maintained in individual metabolism cages for a fasting period of two days and a control period on a diet of evaporated milk. The procedure followed was to administer each drug

in the milk ration after satisfactory control values had been established. Twenty-four hour urine specimens were collected and analyzed for ascorbic acid. Loss of ascorbic acid in the urine samples was prevented by the use of the hydroxyquinoline reagent of Sendroy. In our work 0.05 c.c. of 8-hydroxyquinoline solution (1.45 Gm. of 8-hydroxyquinoline in 100 c.c. of 95 per cent ethyl alcohol) and 0.75 c.c. of 5 N sulfuric acid were placed in each flask at the beginning of the collection period. The drug was given to the animals until the ascorbic acid excretion rose to a maximum value, or, if no rise occurred, for eight days or more. Generally the ascorbic acid excretion was followed for several days after discontinuance of the drug in order to determine the rate of decrease.

Ascorbic acid was determined by the method of Highet and West[13] based upon the use of a standardized solution of 2, 6,-dichlorophenol indophenol in xylene. The following modifications in the method were made. Glass-stoppered graduated cylinders of 50 c.c. capacity were used in place of test tubes. The standard dye solution, the sample to be determined, and the 0.03 N HCl were measured into the graduates. The stoppers were fastened in place and the graduates shaken in horizontal position for three minutes in a mechanical shaker with a driving wheel speed of 370 r.p.m. In preliminary experiments oxidation of the ascorbic acid was found to be complete in this time. The emulsion of the xylene dye and water layers was broken by transferring the mixture to a 50 c.c. centrifuge tube and sifting anhydrous sodium sulfate on top of the foamy liquid. The tube was then stoppered and centrifuged for five minutes at 1,900 r.p.m. The xylene dye layer was poured off and read in a photoelectric colorimeter.

RESULTS

Benadryl administered in amounts of 10 mg. or more per day caused a rise in ascorbic acid excretion within the first twenty-four hours. Maximum excretion was reached in five to eight days and normal values were again obtained within three to four days after the drug was discontinued. In one series in which the initial daily dose of Benadryl was 6 mg., little increase was noted until the dose was doubled and maximum excretion was not reached until the dose had been increased to 24 milligrams.

Benadryl caused the usual rise in excretion of ascorbic acid in rats which had shown no increase during periods on Histadyl and Neo-Antergan.

After administration of Thephorin and Pyribenzamine, ascorbic acid excretion rose within forty-eight hours and reached a maximum in fourteen days. However, initial consumption of milk was small and intake of the drug did not reach 25 mg. per day until six days of the experimental period had elapsed.

Trimeton in amounts of 10 to 15 mg. daily caused increased excretion of ascorbic acid within seven days and levels returned to normal in three days after discontinuance of the drug. The animals would not take quantities of milk containing larger doses of the drug.

Histadyl, Neo-Antergan, and Antistine caused no appreciable rise in ascorbic acid excretion.

The results of an experiment on Histadyl and Benadryl, given in Table I, are representative and show the individual variations during the control and experimental periods. In this experiment the Histadyl period served as the control period for Benadryl since Histadyl was without effect. Other experiments were run in which Benadryl, following a simple control period, gave similar increases in ascorbic acid excretion.

Fig. 1 summarizes the findings on the various drugs. The plots indicate the average total excretion of ascorbic acid per rat during the last five days of both the control and experimental periods.

Animals were autopsied upon termination of the experiments. In general, pathologic conditions were limited to rather frequent respiratory infections which apparently were due to maintenance in small cages that restricted exercise. Several animals of Series IV and V showed lowered white blood cell counts.*

TABLE I. THE EFFECT OF HISTADYL AND BENADRYL UPON THE URINARY EXCRETION OF ASCORBIC ACID BY RATS

DATE	RAT NOS.					
	13	14	15	16	17	18
Control period						
1/14/48	1.0	0.6	0.9	0.9	0.3	0.5
1/15/48	1.5	1.4	2.1	2.3	0.7	0.8
1/16/48	1.4	1.2	1.7	2.3	0.6	0.8
1/19/48	1.6	1.4	1.3	1.7	0.5	0.9
1/20/48	1.4	1.9	1.5	2.0	0.7	1.1
1/21/48	1.6	1.4	1.3	1.7	0.5	--
Average	1.4	1.3	1.5	1.8	0.55	0.82
18 mg. Histadyl per day						
1/22/48	1.6	2.2	2.0	2.3	0.8	1.1
1/23/48	1.1	1.5	1.4	2.3	0.8	1.0
1/26/48	0.6	0.5	0.9	1.3	0.3	0.6
1/27/48	0.8	0.6	1.4	1.7	0.4	1.0
1/28/48	0.9	0.9	1.4	1.5	0.5	0.9
1/29/48	1.3	1.4	1.9	1.4	0.9	1.4
1/30/48	1.4	1.5	1.9	2.1	1.2	1.5
2/ 2/48	1.2	1.3	1.5	1.8	0.4	0.7
Average	1.1	1.2	1.6	1.8	0.70	1.0
18 mg. Benadryl per day						
2/ 3/48	1.5	2.2	1.6	2.0	0.6	0.8
2/ 4/48	2.0	3.2	2.5	2.3	1.0	1.8
2/ 5/48	2.7	2.6	2.9	3.0	1.2	2.4
2/ 6/48	3.3	3.3	3.2	2.7	1.7	2.6
2/ 9/48	8.8	8.4	7.2	7.2	5.8	9.6
Average	3.7	3.9	3.5	3.4	2.1	3.4
Benadryl discontinued						
2/10/48	4.2	5.0	4.4	4.2	2.8	4.4
2/11/48	2.8	3.7	2.8	3.1	1.9	1.9
2/12/48	1.7	1.9	3.4	3.9	1.6	2.1
2/18/48	1.2	1.4	2.5	2.1	1.2	1.4

Values represent milligrams per twenty-four hours.

*The writers are indebted to Dr. Frank B. Queen of the Department of Pathology for the autopsies.

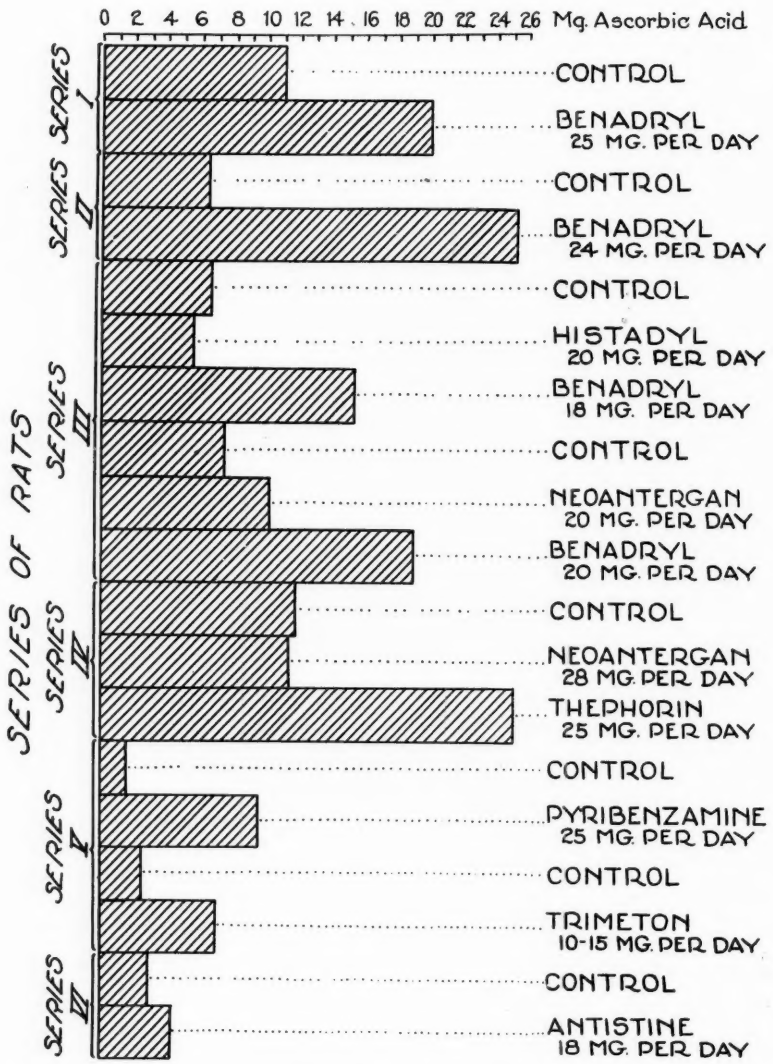


Fig. 1.—Average total excretion (in milligrams) of ascorbic acid in last five days of period.

SUMMARY

1. The results of our experiments show that Benadryl, Thephorin, Pyribenzamine, and Trimeton stimulate ascorbic acid synthesis in the rat while Neo-Antergan, Histadyl, and Antistine have little or no effect.

2. The stimulating action did not correlate with the narcotic effects of the drugs since Thephorin is somewhat stimulating and yet caused as much increase in ascorbic acid excretion as did Benadryl.

The writers are indebted to Mr. Bryce McMurray for technical assistance.

REFERENCES

1. Holmes, H. N., Campbell, K., and Amberg, E. J.: The Effect of Vitamin C on Lead Poisoning, J. Lab. & Clin. Med. **24**: 1119, 1939.
2. Vedder, E. B., and Rosenberg, C.: Toxicity of Vitamin A, J. Nutrition **16**: 57, 1938.
3. Drake, M. E., Gruber, C. M., Haury, V. G., and Hart, E. R.: The Effects of Sodium Diphenyl Hydantoinate (Dilantin) on the Blood Ascorbic Acid Level in Guinea Pigs, J. Pharmacol. & Exper. Therap. **72**: 383, 1941.
4. Peters, R. A., and Davenport, H. W., in Luck, J. M.: Vitamin C, Annual Review of Biochemistry, Stanford Univ. Publ., Univ. Series, M. Sc. **7**: 325, 1938.
5. King, C. G., in Luck, J. M.: Vitamin C, Annual Review of Biochemistry, Stanford Univ. Publ., Univ. Series, M. Sc. **8**: 392, 1939.
6. Hamil, B. M., Reynolds, L., Poole, M. W., and Macy, I. G.: Minimal Vitamin C Requirements of Artificially Fed Infants, Am. J. Dis. Child. **56**: 561, 1938.
7. Rinehart, J. F., Greenberg, L. D., Baker, F., Mettier, S. R., Bruckman, F., and Choy, F.: Metabolism of Vitamin C in Rheumatoid Arthritis, Arch. Int. Med. **61**: 537, 1938.
8. Harris, L. J., Passmore, R., and Pagel, W.: Influence of Infection on the Vitamin C Content of the Tissues of Animals, Lancet **233**: 183, 1937.
9. Kaiser, A. D., and Slavin, B.: The Incidence of Hemolytic Streptococci in the Tonsils of Children as Related to the Vitamin C Content of Tonsils and Blood, J. Pediat. **13**: 322, 1938.
10. Musulin, R. R., Tully, R. H., III, Longenecker, H. E., and King, C. G.: Vitamin C Synthesis and Excretion by the Rat, J. Biol. Chem. **129**: 437, 1939.
11. Longenecker, H. E., Musulin, R. R., Tully, R. H., III, and King, C. G.: An Acceleration of Vitamin C Synthesis and Excretion by Feeding Known Organic Compounds to Rats, J. Biol. Chem. **129**: 445, 1939.
12. Longenecker, H. E., Fricke, H. H., and King, C. G.: The Effect of Organic Compounds Upon Vitamin C Synthesis in the Rat, J. Biol. Chem. **135**: 497, 1940.
13. Highet, D. M., and West, E. S.: A Procedure for the Determination of Ascorbic Acid Based Upon the Use of a Standardized Solution of 2, 6-Dichlorophenol Indophenol in Xylene, J. Biol. Chem. **146**: 655, 1942.

LOCAL INHIBITION OF HISTAMINE FLARE IN MAN

A Method of Bioassay of Antihistamine Drugs*†

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IT WAS felt that a simple, yet reliable, method of assay of the therapeutic action of antihistamine drugs would facilitate their preliminary appraisal and permit better selection for more time-consuming therapeutic trials. It is now pretty generally agreed that there is a lack of sufficient correlation between many types of animal assay and therapeutic results. Although clinical trial is the ultimate measure of the value of a therapeutic procedure, subjective determination of therapeutic results in man as a sole means of evaluation offers a number of difficulties. Variations such as the amount of pollen in the air, the season, the locale, psychogenic factors, and the general vacillations in the course of allergic disease, and even the individual observer's attitude, may influence the results. Clinical trial consumes a long period of time and requires a large number of patients.

It is reasonable to assume that any objective bioassay of an antihistamine drug on man would be more applicable to its potential therapeutic activity. Since localized edema is one of the major manifestations of the allergic reaction, it may be expected that a quantitative tritration of the inhibition of this edema might give an estimation of the therapeutic activity of this drug in man.[1] Assuming that the allergic wheal is due in the main to the action of released histamine, it would be fair to infer that titration of the inhibiting power of these compounds on the wheal produced by histamine locally applied to the skin would constitute an evaluation of the antiallergic activity of the drug.

PRELIMINARY PROCEDURE

It has been known for some time that histamine produces a local skin response. In using this local response as a basis for quantitative experimentation, the first problem was to evaluate the variability of the quantitative histamine response in subjects.[2] With the technique we adopted in producing histamine wheals, we found that comparisons of their size were grossly inaccurate. In large part this was due to the small size of many of the wheals. We noted, however, that the size of the flare was a function of the concentration of the histamine and was relatively easy to measure. We performed a large number of experiments which confirmed this observation and its constancy. We noted that the prior application of the antihistamine drug at the site of the histamine application not only inhibited the flare, but that the inhibition was proportional to the concentration of the drug. We are aware of

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the fact that the wheal is regarded as the direct result of the histamine action on the vessels whereas the flare is the indirect effect or the axone reflex. Nevertheless, on the basis of the above quantitative observations, we felt justified in assuming that in measuring the flare and its inhibiton we were measuring antihistamine activity. We found that individual variability was marked, but that these variations did not depend primarily on such factors as age, sex, the presence of atopy, or environmental conditions. We hope to present the findings on these variables at another time, but suffice it to say here that for the purpose of the studies on antihistamine bioassays, these variables were circumvented by comparing assays on the same subjects and preferably at the same time.

The second major problem was to evaluate the variability in histamine. It had been our impression that histamine would deteriorate with age. This deterioration was variable and more likely to occur rapidly at room temperature. The alkalinity of the solutions from their contact with glass was first regarded as the reason for this deterioration. Because of irregularities in deterioration even after solutions were acidified to pH 5, we were led to seek for some other explanation for the inactivation of histamine. Bacterial counts made on the histamine solutions which had deteriorated, and compared with solutions which had remained stable, showed that the former contained large numbers of bacteria. A culture of these same bacteria inoculated into a freshly prepared histamine solution and incubated at room temperature produced marked inactivation of the histamine as compared to uninoculated histamine solutions prepared at the same time. This demonstrates that bacterial contamination may be one important factor in the deterioration of histamine. Whether or not it is the only factor still remains to be proved.

The site of testing was one of the early problems to be considered. The volar surface of the forearm was used in the beginning but it was found that this site is not as sensitive as the back. The site finally chosen included the area from about the third dorsal vertebral spine to the eleventh, and up to 15 cm. on either side of the midline, depending upon how many columns were needed.

Another problem was the method of local application of histamine and the antihistamine compounds. After some experience with intracutaneous and cutaneous techniques, it was felt that the latter had the advantages of simplicity, sharper end point, and less pain and irritation. Irregularities in the length of the scratch, resulting in irregularities in the size of the reaction, led us to seek a simple means of producing a uniformly sized break in the skin. This was finally accomplished by utilizing a piece of hollow steel tubing, the sharpened end of which was 2 mm. in diameter. Attempts at standardizing the pressure of such an instrument against the skin was abandoned because of technical difficulties and because of differences in skin thickness. We found that gauging the amount of pressure of this tube with slight rotation against the skin resulted in uniform areas of breaks in the skin on which our histamine and antihistamine solutions could be placed.

The size of the drops of the solutions applied to the skin sites was the next problem. A dropper was devised which would deliver a drop of uniform size. The objections to this device were that it encouraged cross-contamination of the solutions, and that the time consumed with repeated applications of these drops interfered with the rapidity of titration necessary for an accurate assay. Experimentation with different size drops convinced us that the usual variations in the size did not vary the size of the reaction. We finally adopted the technique of using an ordinary small dropper.

One of the most difficult problems was to arrive at a workable and sensitive range of dilutions of the histamine and antihistamine solutions. Our first range of histamine dilutions was from 1:1,000 to 1:64,000, while the antihistamine range began at 1:50 or stronger.[3] We found that these ranges were objectionable because they did not produce the best end points. In our inhibition experiments we first used the concentration of histamine which had produced maximal reactions, but later found that those giving half-maximal response yielded more reliable results. The choice of the half-maximal response was determined by the following procedure. On each of 3 series of sites which had been pretreated by serial dilutions of the antihistamine, varying concentrations of histamine were applied. On one series was applied a solution of histamine giving a maximal flare; on a second, histamine giving a flare half of the maximal size; and on the third, histamine giving minimal response. It was determined that half-maximal response resulted in a degree of inhibition which was best suited for comparison in the series of antihistamine drugs with which we worked.

TECHNIQUE

The actual technique we adopted for the bioassay of antihistamine drugs by means of their local inhibiting effect on histamine was as follows:

Selection of subjects was made carefully because some patients were nonreactive, some were too highly reactive, and others were too dark-skinned for the flare to be seen. We chose adults almost entirely, chiefly because the size of the children's backs was too small to allow sufficient space for the number of drugs in each series. The same subjects were utilized as much as possible for repeated tests. Because of greater comfort for the patient and to avoid the running of drops off the sites, the prone position was used almost exclusively. From 20 to 40 subjects were tested for each series of drugs.

As indicated above, the back was used for all assays. The different drugs were not always placed in the same order on the back so that a difference in reactivity of different areas of the skin could to some extent be neutralized by this randomization.

Solutions of histamine phosphate were employed in dilutions of 1:8,000 in 100 per cent increments to 1:512,000, in terms of histamine base. The diluent was distilled water to which merthiolate of a final concentration of 1:100,000 was added. Antihistamine compounds were dissolved in distilled water and used in dilutions of 1:3,200 in 100 per cent increments to 1:204,800.

Breaks in the skin were made with the sharpened hollow steel tubing deep enough to cut through the epidermis without drawing blood, and with as little trauma as possible. Cuts were made in columns 4 to 5 cm. apart equidistant from the vertebral spines on each side. In each column cuts were made 4 to 5 cm. apart at the top and 2 to 3 cm. apart toward the bottom to allow for the larger flares which appeared at the top due to the more concentrated histamine or to less inhibition from the weaker antihistamine solutions.

The histamine responsiveness of the subject was ascertained by making a series of applications of histamine drops on a row of cuts on the back, with the highest concentration (1:8,000) at the top. The histamine was given sufficient time to produce the optimum reaction. On an adjacent row of cuts drops of the serial dilutions of an antihistamine were placed, with the lowest concentration (1:204,800) at the top. Usually 3 or more such antihistamines were applied on parallel series of cuts and Pyribenzamine was included as a standard. The antihistamine compounds were allowed to remain on the cuts for 10 minutes,

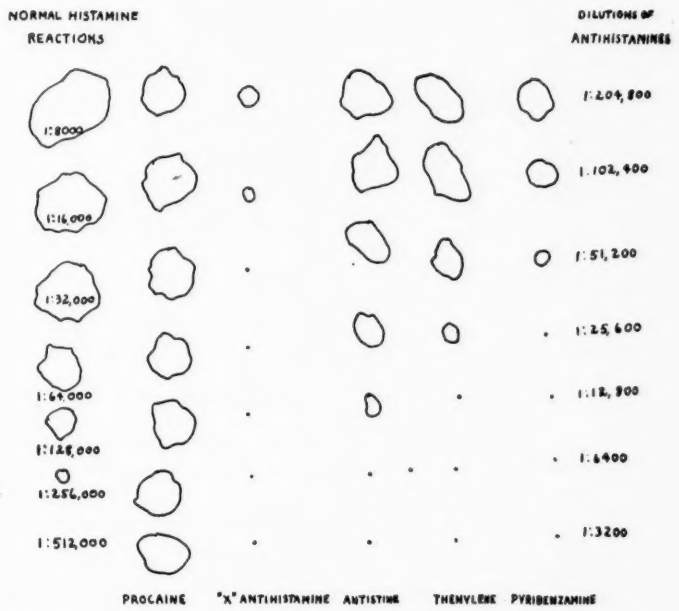

Fig. 1.—Quantitative inhibition of histamine reaction. Sensitivity of the subject is determined by titration of histamine dilutions applied to a series of scratches on the back (column at left). Dilutions of antihistamine drugs were placed on several abraded areas on the same subject at the same visit. After 10 minutes the drugs were washed off, and a drop of a concentration of histamine which gave half-maximal flare (1:64,000 in this case) was applied to each site. The flares occurring about 10 minutes later were outlined with a ballpoint pen and the tracings transferred on paper. Different degrees of inhibition with variuos drugs are noted in the figure above. The above assay is repeated on 20 to 40 subjects and results averaged.

since it was found earlier that at this period the optimal inhibiting effect was produced. Subsequent experience has indicated that this arbitrary limit may not be proper for exceptional drugs which are slow in their onset of action, and that this difference may result in misinterpretations.

Ten minutes after application the antihistamine solutions were washed off, using care to wash from the direction of the more dilute toward the more concentrated. A drop of histamine solution of that concentration which gave in

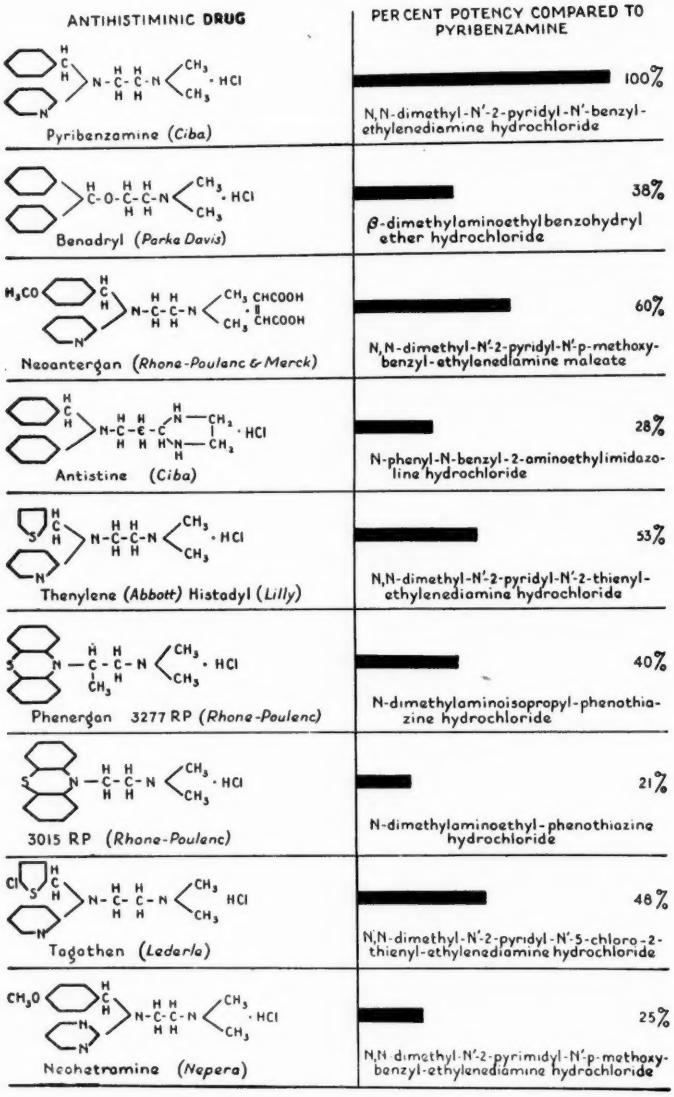

Fig. 2, *A*.

that particular subject a flare about one-half the size produced by the highest concentration was applied to each of the pretreated sites. The histamine drops were allowed to stay on an equal period of time, then washed off. The resulting flares were outlined with a ballpoint pen and the tracing transferred to paper by pressure.

The end point of inhibition of histamine differed on the same individual at the same time with different antihistamine drugs. This difference is a measure of the difference in ability of the drug to inihibit histamine locally. The places of complete and partial inhibition of hitsamine by a given antihistamine drug were noted and compared with the places of complete and similar degree of

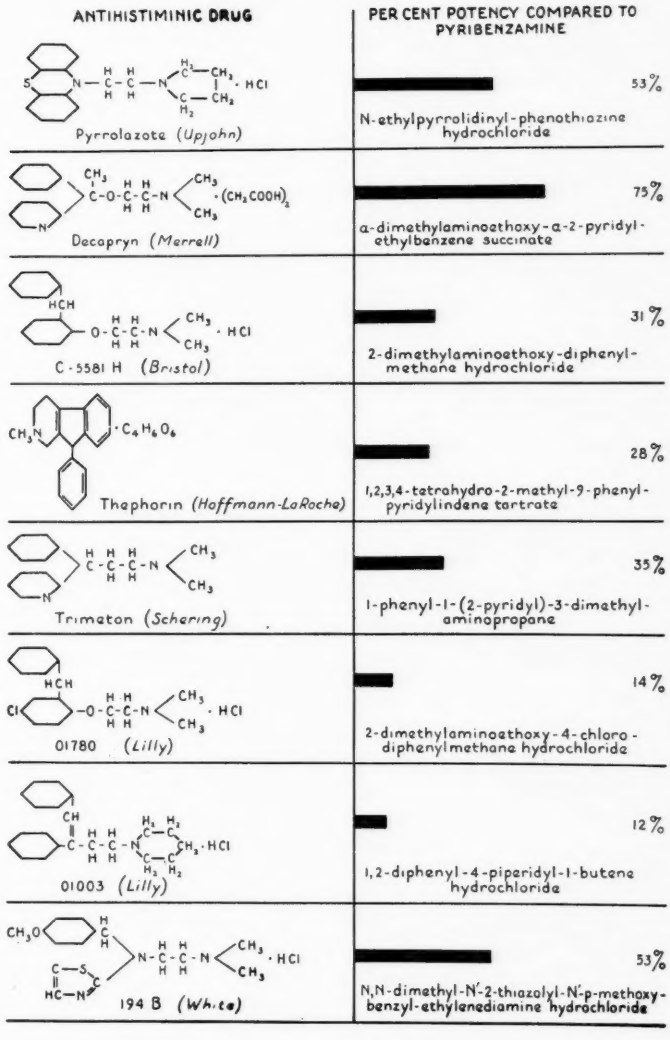

Fig. 2, *B*.

partial inhibition of histamine by Pyribenzamine. Such a comparison results in a difference which may vary from one to more places in the antihistamine dilution. Such "place differences" in 20 or more subjects were added and averaged, giving the average "place difference" between the unknown antihistamine drug and Pyribenzamine. Potency was then computed in per cent potency of Pyribenzamine by plotting average place difference against the concentration of antihistamine drug in relation to the standard (Pyribenzamine).

The results of this assay are shown in Fig. 2.

DISCUSSION

The results as reported are indicative of the potency of these drugs in so far as it measures their ability to inhibit the histamine flare when applied

locally. This inhibition is not due in any way to the local or topical anesthetic effect of the antihistamine drugs. This was indicated by the failure to obtain any inhibition of the flare with procaine and Pontocaine hydrochloride in concentrations as high as one per cent, using the same procedure as employed with the antihistamines.

This interpretation may err in that there may be differences in local absorption or in rapidity of action of the different antihistamine drugs. Differences between local effect and systemic effect are also possible because of metabolic changes on the drug or because of differences in absorption from the gastrointestinal tract. To throw further light on this phase, we have made serial histamine titrations at intervals following the oral ingestion of the drug. We have been able to study comparative degrees of activity and duration of action by this means. The outstanding difficulty with the oral method of assay is that its accuracy is much less than the local method, probably because the quantitative changes in the histamine reactions are of a lesser order. Since this phase of the work is not yet completed, we shall reserve the results for a future report. Recently, Serafini[4] reported a study comparing the local histamine-inhibiting effect of several antihistamine drugs administered orally. Although the antihistamine drugs inhibit the local allergic reaction, it is realized that the histamine reaction is not necessarily synonymous with it, and experiments are under way to determine the relationship between the two.

Clinical therapeutic results agree in the majority of instances with the results obtained by this method of bioassay. Out of 17 antihistamine drugs with which we have had clinical experience, 15 seem to agree well. In the case of Thephorin and 3277 RP, the clinical results may be better than would be inferred from the flare inhibitions, although there is no certainty about this. Recently, Schwartz and Wolf[5] reported a study of inhibition of histamine and ragweed wheals by local application of antihistaminics and concluded that the latter showed little variation. Since in their method they employed one strong concentration of histamine (1:1,000) and one strong concentration of an antihistaminic (5 per cent), their tests cannot be considered quantitative in any sense of the word.

Many other compounds of possible therapeutic value were investigated by the local method, but these have not been given adequate therapeutic trial. However, on the basis of results obtained, most of these compounds were of low potency. We feel that since this method of assay does agree so well with our clinical results, much valuable time consumed by the therapeutic trial of useless drugs could be eliminated by first subjecting a possible antihistamine compound to this type of screening, and perhaps best combined with the oral assay method, and thereby allowing more time for more extensive testing of the more promising compounds.

SUMMARY

1. A method of bioassay using a technique of local inhibition of the histamine flare by antihistamine drugs is described.

2. The results of this bioassay are given in terms of the relative potency of such drugs compared to Pyribenzamine as a standard.

3. The results of the bioassay agree quite well with the therapeutic results in most instances, and this technique has been of value in the preliminary assay of antihistamine drugs. Only more extensive application of this method in comparison with larger clinical trials will determine whether this type of assay is of sufficient trustworthiness. Other techniques are being examined.

REFERENCES

1. Friedlaender, S., and Feinberg, S. M.: Histamine Antagonists. III. The Effect of Oral and Local Use of β-Dimethylaminoethyl Benzhydryl Ether Hydrochloride on the Whealing Due to Histamine, Antigen-Antibody Reactions, and Other Whealing Mechanisms. Therapeutic Results in Allergic Manifestations, J. ALLERGY **17**: 129, 1946.
2. Sherman, J., and Walzer, E. H.: The Responsiveness of Human Skin to Histamine Introduced by the Electrophoretic Technic, J. Invest. Dermat. **9**: 187, 1947.
3. Feinberg, S. M., and Bernstein, T. B.: Histamine Antagonists. X. A New Antihistamine Drug, 2-[α-Dimethylaminoethoxy)-α-Methylbenzyl]-Pyridine Succinate (Decapryn Succinate); Experimental and Clinical Results, J. Lab. & Clin. Med. **33**: 319, 1948.
4. Serafini, U.: Studies on Histamine and Histamine Antagonists, J. ALLERGY **19**: 256, 1948.
5. Schwartz, E., and Wolf, J.: Histamine Antagonists. A Comparative Study of Their Effect on Histamine and Allergic Skin Wheals, J. ALLERGY **20**: 32, 1949.

QUANTITATIVE STUDIES IN SKIN TESTING

IV. The Volume-Response Relationship*†

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IN PREVIOUS papers of this series[1, 2] the relationship between the concentration of allergen injected into the skin in specifically sensitive individuals and the response so elicited was studied. The variability of the response has led us to examine more closely factors other than concentration, which might affect the size of the wheal. In the previous work it was attempted to keep the volume injected constant while the concentration varied. Realizing that there was a large inadvertent variability in the amount injected, it was considered that this might help account for the irregularity in the size of the wheal at a constant concentration.

This paper reports the result of an investigation of the effect on wheal size of systematically varying the volume injected endermally while keeping the concentration of allergen constant. In this study not only the widest diameter of the wheal was measured but the total area was determined. It was thus possible to obtain an empirically derived relationship between the mean maximum wheal diameter and the mean total area.

METHODS

In order to inject accurately measured volumes, a specially designed syringe of stainless steel construction was used. The barrel and plunger were accurately machine tooled to fit with a tolerance of $\frac{1}{10,000}$ of an inch. A thin bar parallel with the plunger fitted into a hole in the guard on the barrel to steady the plunger and prevent buckling. The calibration markings were engraved on this guide rod. The syringe was calibrated with mercury to deliver volumes between 0.005 ml. and 0.078 ml. in intervals of 0.005 ml.

At a standard time of ten minutes after the injection of the allergen the resultant wheals were outlined directly on the skin of the subject with India ink diluted 50 per cent with alcohol, using a fine pointed pen. After the ink dried, the outlines were transferred from the skin to Scotch tape. The Scotch tape was firmly pressed over the wheal outline and then pulled off the skin. The inked outline came off on the sticky surface of the tape. The tape with the outline was then either pasted in a notebook or on a glass lantern slide.

A lantern slide was prepared of a grid accurately ruled in square millimeters. The outline of the wheals placed on lantern slides was projected with the slide containing the ruled grid onto a wall by means of a lantern slide projector. The equally magnified image of the wheal outline and the grid allowed a relatively easy measurement of the area of the wheal by counting the

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†The expenses of this investigation were in part defrayed by funds from the Asthmatic Children's Aid.

squares enclosed by the outline. To facilitate this counting, the grid was ruled off not only in square millimeters but also in heavier lines enclosing 25 mm. square areas.

The subjects used in the experiment were all clinic patients undergoing treatment for ragweed pollinosis. Several different concentrations of a mixed giant and dwarf stock extract were used although only one concentration was tested at any one experimental period. The various volumes used, 0.005, 0.01, 0.02, 0.04, 0.06, and 0.078 ml., were injected into the volar surface of one or both forearms of the subjects. Every subject received every volume. To eliminate the effect of site differences, the placing of the different volumes on the sites of the forearms was randomized.[2]

RESULTS

The maximum diameter of the wheal outline obtained from the Scotch tape transfer was measured with calipers accurate to 0.1 millimeter. Later the area of the wheal outlines was determined as described. The wheal diameter and wheal areas for a given injection volume of a given experimental day were averaged. The respective average wheal diameters and areas so obtained are plotted in Fig. 1. The solid line through the points is the curve of the equation $y = 0.533D^{2.00 \pm 0.00822}$ found to fit the points.

It is possible, using the equation, to predict the average area of the wheal from the measurement of the average maximum wheal diameter with an error of 10 to 15 per cent. This is known to hold only between the limits studied, that is, an average maximum wheal diameter of 3 to 18.5 mm., giving areas from 6 mm. square to 152 mm. square.

Fig. 2 shows the result of four different experiments in which the change of volume at constant concentration was investigated. The individual values of each curve are the averages from four to six subjects. A different concentration of allergen and groups of somewhat different composition were used for each curve. Increasing the volume injected from 0.005 to 0.01 ml. increased the size of the wheal 1.2 to 1.5 times; while increasing the volume injected from 0.01 to 0.02 ml. increased the wheal size from 1.2 to 1.7 times. The interpretation of this in terms of the changes in concentration at constant volume, which would be required to give similar changes in wheal size, will be left to the discussion.

In the routine use of endermal testing, the amount injected is usually judged by the size of the initial bleb with the corollary assumption that equal size blebs give equal size wheals, other factors being constant. It then became of interest to investigate what type of correlation between initial bleb and final wheal actually could be demonstrated.

The outline of the initial bleb was made immediately after the removal of the needle from the site of injection; the final wheal was allowed to develop, outlined, and the two outlines taken off on the adhesive surface of Scotch tape. In a number of instances the initial bleb was outlined and the outline pulled off before the wheal developed. Comparing the initial bleb outlines before and after the raising of the wheal revealed no differences. A small amount of fluid

leaked out from the puncture on withdrawal of the needle. This unavoidable and variable amount increased as the volume injected rose above 0.04 milliliter. In Fig. 3 the average initial bleb area is plotted against the resultant wheal. As can be seen from the curves of the three experiments there is almost a linear relationship between initial bleb and final area at constant concentration.

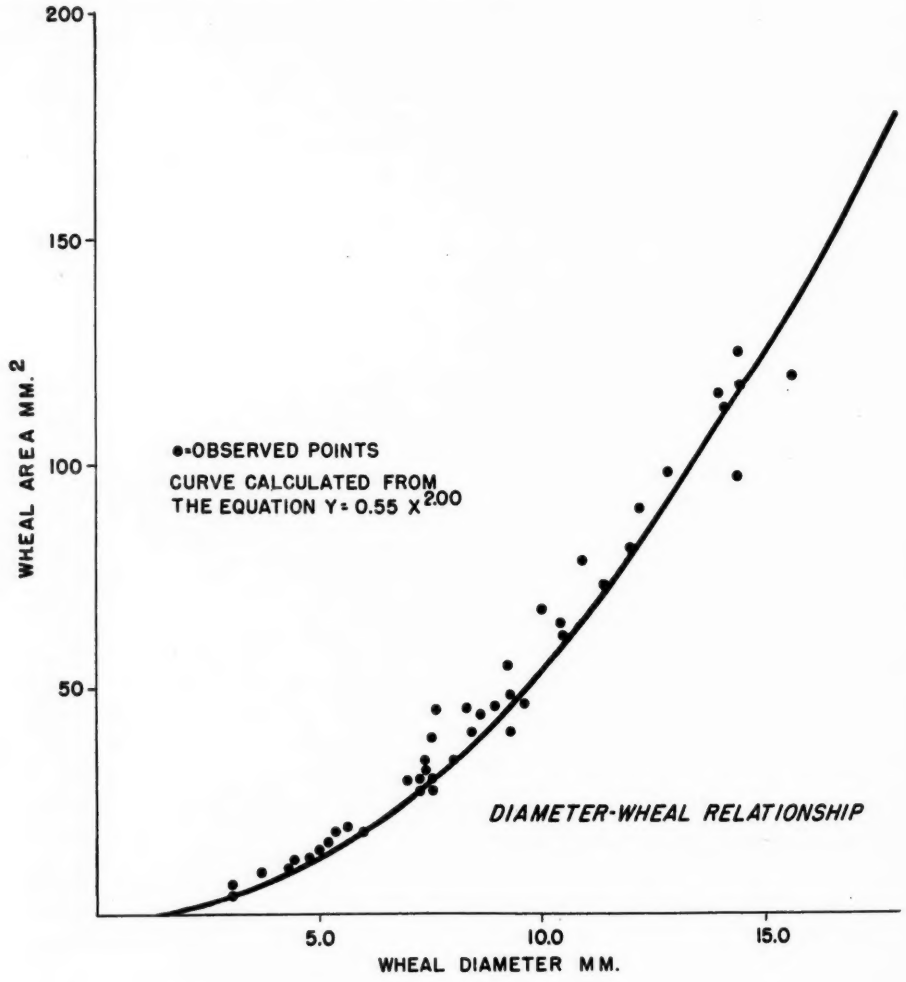

Fig. 1.

DISCUSSION

The syringe described in this paper was found adequate for the work reported here. In the course of this investigation, however, deficiencies in the design of the syringe became apparent. Constant use resulted in a torsion of the guide rod and plunger with a loss of free movement of the plunger in the barrel. A micrometer adjustment for 0.25 ml. tuberculin-type syringes was designed for all subsequent work. This will be reported later.

As shown in Fig. 1, the relationship between average maximum diameter and average wheal area can be expressed by an equation $A = cD^s$ where A is

wheal area, D is wheal diameter, and c and s are constants. In one of the preceding papers of this series the relationship between concentration P and average wheal diameter D was found to be of the same form, $D = aP^b$ where a and b were constants. Using the average value for b of 0.133, found in the previous work,[2] the relationship between wheal area and concentration would become $A = aP^{0.266}$ in which a is a constant which depends on the sensitivity of the group being tested. If this conclusion were found to hold, one might be able to double the accuracy of the assay by measuring areas instead of wheal diameters. This would be true since the error of the assay is directly proportional, all other things being equal, to the slope, b, of the dose-response curve. Whether this would be worth the extra work involved would of course depend on the needs of the investigator.

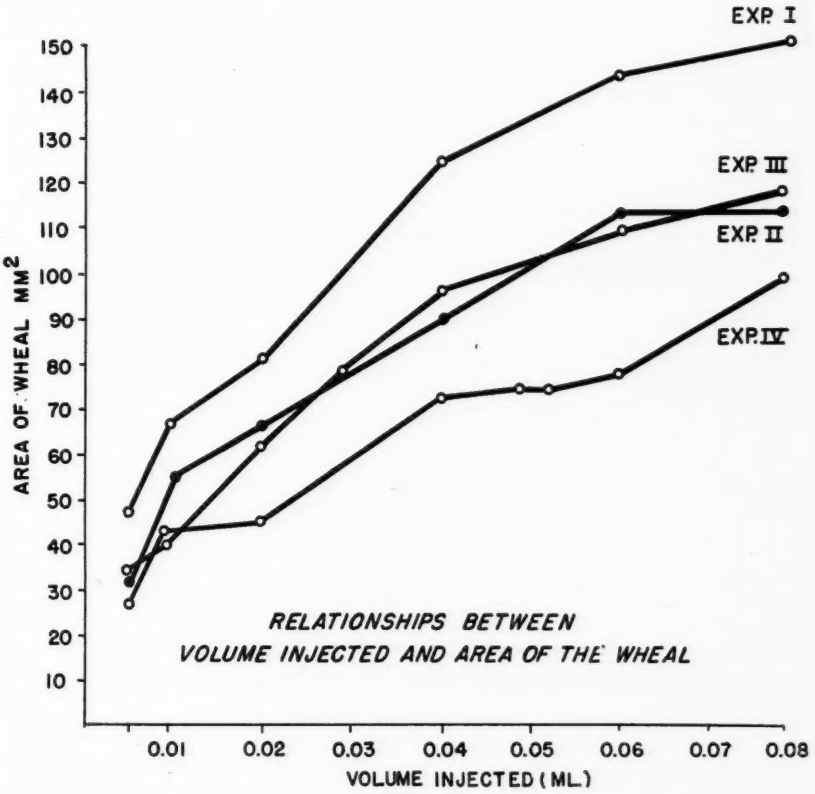

Fig. 2.

The magnitude of the effect of the volume injected on the size of the resultant wheal is illustrated in Fig. 2. If one expresses this volume effect in terms of the change in concentration required to give the same change in wheal size one can obtain perhaps a clearer estimate of the magnitude of this volume effect. To do this the expression $D = aP^b$ was used,[2] with a value for b of 0.133. One then can calculate that increasing the volume from 0.005 ml. to 0.01 ml. is equivalent to increasing the concentration about 160 per cent; while increasing

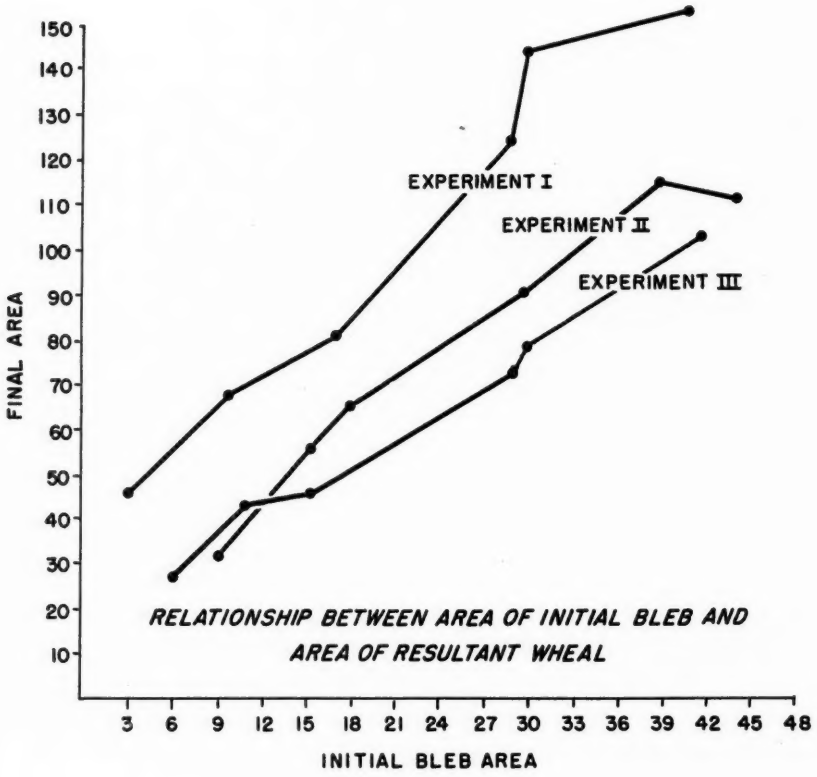

Fig. 3.

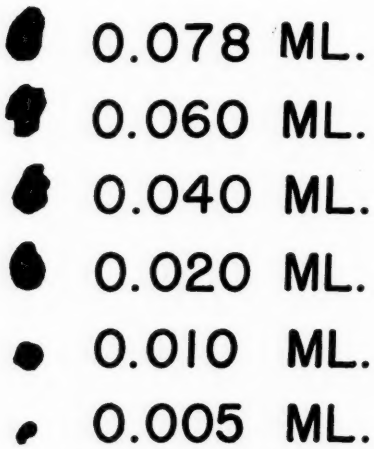

Fig. 4.—Tracings of immediate bleb size for the indicated injection volumes.

the volume from 0.01 to 0.02 ml. is equivalent to increasing the concentration by approximately 300 per cent. These values are of course approximations, but certainly they give the order of magnitude. Under routine conditions such variation of injection volume is probably not uncommon.

Even with reasonably accurate control of the volume, as in this work, variation was found which was greater than desired and which could not be attributed to differences in individuals or sites. This suggests that other factors influence the wheal response. One of these factors is the depth of the injection. This will be investigated in the near future.

It was surprising to us how large a wheal was produced by the endermal injection of 0.005 or 0.01 milliliter. In the directions for endermal skin testing given by most authors, the injection of 0.01 to 0.02 ml. of allergen is advised. It was our impression that endermal injections which we had heretofore thought to be between 0.01 and 0.02 ml. were actually between 0.005 and 0.01 milliliter. Fig. 4 shows the outlines of the initial bleb, natural size, corresponding to the given volumes injected.

SUMMARY

1. A syringe has been described which has served for the accurate endermal administration of small volumes of fluid.

2. A method for obtaining accurate outlines of wheal areas has been described.

3. The relationship between average maximum wheal diameters and wheal areas has been quantitatively studied. The importance of the volume injected of an allergen has been quantitatively evaluated and the necessity for its control stressed.

REFERENCES

1. Becker, E. L.: Quantitative Studies in Skin Testing. I (A), J. ALLERGY **19**: 108, 1948.
2. Becker, E. L., and Rappaport, B. Z.: Quantitative Studies in Skin Testing. II, J. ALLERGY **19**: 317, 1948.

SPIROMETRIC EVALUATION OF ORTHOXINE IN BRONCHIAL ASTHMA*

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FOLLOWING the release of Benadryl for commercial distribution, a very large number of antihistaminic drugs have appeared. The medical literature contains numerous reports of the clinical evaluation of these substances in a variety of presumably allergic phenomena. Although the major interest has centered around antihistaminic agents, new sympathomimetic-like substances also have been released by pharmaceutical firms for use in bronchial asthma and allied disorders. The Lung Station of Charity Hospital at New Orleans has been interested in the objective evaluation of these drugs in acute attacks of bronchial asthma and has previously reported on the use of Benadryl[1] and "Ethyl-Nor-Epinephrine" (Butanefrine),[2] the former an antihistaminic drug, and the latter a sympathomimetic drug.

The psychic factors which operate to some extent in most patients with bronchial asthma are hard to circumvent in the evaluation of any antiasthmatic substance. This is particularly true since the daily newspapers and weekly magazines have published premature and enthusiastic reports. For this reason, and others discussed previously by us,[1] we have limited ourselves to the spirometric evaluation of antiasthmatic drugs in patients with moderately acute attacks of predominantly extrinsic bronchial asthma under controlled environmental conditions. Such a procedure does not free the results from psychic factors, but does minimize errors in judgment which occur when the report of the patient is used as the sole basis of evaluation.

Orthoxine† is orthomethoxy-β-phenylisopropyl methylamine hydrochloride and thus belongs among the sympathomimetic-like amines. Experiments in the Upjohn laboratories utilizing the isolated, perfused rabbit lung preparation have demonstrated the effectiveness of Orthoxine in overcoming bronchoconstriction produced by pilocarpine, histamine, and acetyl choline. Under these conditions, Orthoxine is a more effective bronchodilator than ephedrine, and less effective than epinephrine. However, experiments on dogs conducted in the same laboratory revealed that Orthoxine possessed only $\frac{1}{2,000}$ the pressor activity of epinephrine and less than $\frac{1}{8}$ that of ephedrine. Orthoxine, being an isopropylamine, is effective following oral administration.

PROCEDURE

Twenty patients with bronchial asthma were selected for study. Patients with moderate or severe emphysema were excluded even when bronchial asthma was a prominent feature of the illness. This was done for reasons which will be discussed in a later report on such individuals.

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†Supplied by The Upjohn Company, Kalamazoo, Mich.

Spirometric studies were performed in the Lung Station where air-conditioning is present. After a control record was obtained, the patient was given 100 mg. of Orthoxine by mouth with two ounces of cool, but not cold, water. Spirometric records were made forty-five minutes and ninety minutes after ingestion of the drug. The blood pressures and pulse rates of seventeen of these patients were recorded at fifteen-minute intervals. The protocol for each patient contained a statement of the time of appearance of subjective relief and the patient's evaluation of its effects. Each patient was questioned concerning such side effects as dizziness, palpitation, weakness, excitement, headache, or nausea. In addition to the measurement of the usual pulmonary volumina, the expiratory differential was determined. As previously described,[1] this measurement denotes the volume, in liters, between the expiratory level of the vital capacity breath and the expiratory level of the preceding breath.

RESULTS

The vital capacity was increased by 25 per cent or more in thirteen of the twenty patients. The maximum increase was 95 per cent. In five patients the increase was between 10 and 25 per cent. One patient whose vital capacity decreased by 13 per cent at the ninety-minute interval showed no significant change in the vital capacity at forty-five minutes but did have a significant increase in the complemental air and expiratory differential at this time. In addition, this patient slept following the forty-five-minute tracing, at which time his attack seemed to be subsiding. However, his attack recurred and became more severe prior to the ninety-minute tracing. This patient experienced definite relief after receiving 0.25 Gm. of aminophylline intravenously. Patient 20 (Table I) obtained neither subjective relief nor significant objective improvement following the ingestion of Orthoxine. This patient did not obtain relief regularly from ephedrine, but did from epinephrine. The vital capacity increased 78 per cent after he was given 0.25 Gm. of aminophylline intravenously.

The reserve air increased in all patients except one. The complemental air was increased in all except four patients. The expiratory differential increased significantly in sixteen of the twenty subjects. Changes in the volume of the tidal air have little significance. The respiratory rate had decreased at the forty-five-minute interval in sixteen patients whereas it increased significantly in one.

Five of the twenty patients stated that they experienced slight or no relief from their attack. Three of these five showed definite objective evidence of improved ventilation. Three of the subjects reported complete relief and an additional seven stated that the result obtained by Orthoxine was as good as that usually experienced after receiving adrenalin or aminophylline. Three patients claimed to have obtained more relief than the objective findings indicated. A summary of the spirometric changes is presented in Table I.

During the ninety-minute period of study, no significant changes in blood pressure were recorded. A slight decrease in both the systolic and diastolic levels was the usual finding, but this change was of an order such that it could

TABLE I. RESPIRATORY MEASUREMENTS

PATIENT	VITAL CAPACITY* (MINUTES)				RESERVE AIR* (MINUTES)				COMPLEMENTAL AIR* (MINUTES)			
	S†	45	90	%‡	S†	45	90	%‡	S†	45	90	%‡
1	1.47	1.92	1.79	+38	.64	.58	.64	−9	1.17	1.47	1.37	+25
2	1.84	2.35	1.92	+33	.60	.81	.60	+35	1.82	1.73	1.35	−26
3	.15	1.15	1.32	+80	.11	.32	.26	+190	.64	.79	1.15	+80
4	1.17	2.09	2.01	+75	.09	.71	.90	+900	1.11	1.28	1.51	+36
5	.90	1.62	1.75	+95	.30	.68	.82	+200	.85	.92	1.45	+70
6	1.43	1.50	1.65	+16	.41	.47	.83	+100	1.20	1.05	1.07	−13
7	2.35	2.18	2.59	+10	.56	.62	.79	+40	1.92	2.04	2.05	+6
8	.98	1.24	1.32	+60	.28	.30	.34	+20	.81	1.05	1.34	+65
9	.84	.77	1.02	+25	.36	.34	.38	+5	.63	.71	.94	+50
10	.77	.88	.79	+14	.21	.33	.15	+55	.66	.69	.66	+1
11	1.05	1.07	1.37	+30	.36	.44	.49	+36	.60	.77	1.03	+73
12	3.06	3.53	3.89	+28	.68	.68	.83	+22	2.71	2.54	3.16	−63
13‖	1.45	1.47	1.26	−13	.75	.77	.60	+6	.75	1.03	1.09	+40
14	1.39	1.77	2.11	+50	.51	.77	.77	+50	1.09	1.60	1.58	+46
15	2.00	2.18	2.22	+10	.43	.60	.49	+40	1.54	1.82	1.90	+25
16	1.09	1.24	1.60	+40	.21	.39	.47	+120	1.07	.98	1.24	+15
17	1.78	1.92	2.44	+36	.49	.53	.64	+30	1.24	1.41	1.99	+62
18	.81	.90	1.13	+40	.28	.34	.28	+21	.73	.81	.91	+25
19	1.75	2.07	2.05	+18	.58	.77	.77	+33	1.17	1.71	1.67	+45
20‖	.88	.86	.90	0	.21	.30	.38	+80	.73	.66	.70	−10

*In liters.
†Control tracing before 100 mg. Orthoxine orally.
‡Percentage (per cent) maximal increase (+) or decrease (−).
§Subjective relief recorded as: +, slight; ++, moderate; +++, marked, comparable to
‖Aminophylline, 0.25 Gm. intravenously after Orthoxine and spirometry.
¶Minus sign indicates the volume by which the patient failed to reach the expiratory

be due to either a mild depressor effect of the drug, or to the recumbent position for ninety minutes, or to greater relaxation resulting from amelioration of the asthma. One patient whose initial blood pressure was 94 systolic and 70 diastolic showed a fall to 70 systolic and 50 diastolic at the ninety-minute interval. This patient was only 13 years of age and reported no symptoms of hypotension.

There was no definite effect on the pulse rate, and no patient noted any palpitation, excitement, depression, dizziness, or nausea. Two patients reported that Orthoxine produced some dryness of the mouth. Several complained of the bitter taste when the pill was not quickly swallowed.

DISCUSSION

In patients with moderate, acute attacks of asthma the ventilatory changes produced by 100 mg. of Orthoxine orally are of a magnitude very similar to those produced by the intramuscular injection of 2 mg. of Ethyl-Nor-Epinephrine (Butanefrine). The changes are similar to those produced by epinephrine and aminophylline, but are neither as rapid in appearance nor as marked quantitatively. Relief of symptoms is ordinarily not manifest until thirty minutes after the ingestion of Orthoxine. The spirometric studies fully substantiate the bronchodilator effect of Orthoxine which has been found in the isolated, perfused rabbit lung. The majority of the patients studied exhibited an increase in the vital capacity, reserve air, complemental air, expiratory differential, and a decrease in the respiratory rate.

FOLLOWING ORTHOXINE

TIDAL AIR* (MINUTES)				MINUTE RESPIRATORY RATE (MINUTES)			EXPIRATORY DIFFERENTIAL* (MINUTES)				SUBJECTIVE RELIEF§ MINUTES	
s†	45	90	%	s†	45	90	s†	45	90	%‡	45	90
.85	.81	.81	−5	24	18	24	.40	.68	.60	+70	+++	+++
.60	.62	.75	+25	33	30	35	.32	1.09	.60	+240	+	+
.51	.51	.79	+55	32	26	29	.06	.19	.45	+650	++	++++
.98	1.37	1.22	+40	24	19	14	.11	.66	.66	+500	0	+
.75	.83	.98	+33	25	18	14	.15	.60	.49	+300	++	++
.68	.66	.72	+4	20	18	21	.24	.43	.71	+195	+++	++
.34	.75	.77	+125	26	20	19	.13	.39	−	+500	++	+++
.39	.30	.30	−23	17	17	19	.12	−.04¶	.07	−130	0	+
.34	.30	.36	−12	27	22	21	−.11¶	.04	−.11¶	+130	+	++
.36	.32	.34	−11	27	21	18	−.17¶	.11	−.21¶	+160	+	+
.49	.55	.39	+12	17	23	20	.34	.10	.41	−70	+++	+++
.71	.88	.85	+24	16	13	13	.47	.75	.85	+80	+	++
.49	.45	.58	+18	18	17	20	.41	.49	.36	+19	+++	0
.45	.49	.47	+9	24	21	19	.26	.38	.75	+230	+++	++++
.51	.43	.28	−45	22	20	22	.38	.32	.32	−16	++	+++
.58	.58	.57	−12	19	19	20	.06	.32	.17	+210	++	++++
.38	.28	.32	−26	20	21	19	.21	.36	.38	+81	+	+++
.34	.32	.34	−6	28	23	25	.09	.17	.30	+230	+	++
.60	.53	.96	+60	22	17	17	.53	.43	.75	+41	+	++
.43	.41	.38	−12	31	21	22	.17	.05	.15	−70	0	0

adrenalin or aminophylline; ++++, complete relief or better than adrenalin or aminophylline.

level of the prevital capacity breath.

The expiratory differential should not be confused with the reserve air. By definition, the reserve air is the volume of air which can be forcibly expired at the conclusion of a normal expiration. On the other hand, the expiratory differential represents the difference, in liters, between the expiratory level of the vital capacity breath and the preceding normal expiration. Consequently, in patients with bronchospasm, the volume for the expiratory differential will be less than the reserve air because of the shift upward of the mid-capacity which takes place with maximal inspiration in these patients. In some instances such patients will not be able to expire with the vital capacity breath to the same level as the previous normal expiration and the expiratory differential will then be expressed as a negative value. In uncomplicated bronchospasm the changes in the expiratory differential following the administration of a bronchodilator are probably more significant than the changes in the reserve air if the spirograms are carefully made.

In connection with the spirometric studies, a number of patients were given Orthoxine three times each day, usually at their request. Some of these patients suffered from bronchial asthma, others from hypertrophic emphysema. It was found that the daily administration of Orthoxine was more effective in keeping the patient relatively free from attacks of asthma than it was in controlling alone the acute attack. The dosage used for chronic medication has varied from 50 mg. three times a day to 200 mg. three times a day. In over fifty such patients, there has developed no instance of cutaneous sensitivity or significant side reaction other than a few complaints of dryness of the mouth and occasional mild anorexia.

Our results suggest that Orthoxine possesses the advantages of being a drug whose action is as prompt as ephedrine when both are administered orally, is almost completely free from unpleasant side reactions after a dosage which is therapeutically effective, and does not require parenteral administration. Ephedrine is a vasopressor and central nervous system excitant, Orthoxine is not.

SUMMARY

1. Spirometric studies which were performed on twenty patients with moderate acute attacks of bronchial asthma indicate that orthomethoxy-β-phenylisopropyl methylamine hydrochloride (Orthoxine) is an effective bronchodilator and antiasthmatic drug.

2. There was no definite effect on the heart rate or the blood pressure following the ingestion of 100 mg. of Orthoxine, and no undesirable side effects were noted.

REFERENCES

1. Levy, L., II, and Seabury, J. H.: Spirometric Evaluation of Benadryl in Asthma, J. ALLERGY **18**: 244, 1947.
2. Levy, L., II, and Seabury, J. H.: Spirometric Evaluation of "Ethyl-Nor-Epinephrine" in Bronchial Asthma, J. ALLERGY **19**: 58, 1948.

FATAL ANAPHYLACTIC SHOCK FOLLOWING THE ADMINISTRATION OF A PROTEIN DIGEST (AMIGEN)*

A Case Report

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IN A REVIEW of the literature through 1947, we were able to find only four deaths due to the injection of protein hydrolysate. The first case, as reported by Hopps and Campbell,[1] was that of a patient operated upon for carcinoma of the cystic duct. The cystic duct and gall bladder were removed, the common duct ligated, and the hepatic artery ligated and severed. Postoperatively, there was a steady downhill course with a precipitant drop in the serum proteins. Two days later, 200 c.c. of Amigen were injected intravenously, followed by a severe chill and death one hour later. Post-mortem examination revealed extensive liver damage as would be expected.

Curreri and associates[2] report the second fatality. A supposedly healthy individual suffering only from an inguinal hernia was given Amigen during a metabolic study on three successive days. On the third day, after receiving 150 c.c., the patient developed chills, headache, vomiting, and a fever of 106° Fahrenheit. He expired 40 hours later. The autopsy showed generalized congestion of all organs, cerebral edema, hyperplasia of the splenic pulp cords, and extensive liver damage.

Elman[3] mentions a fatal case reported to him, in which, following the intravenous administration of 15 to 20 c.c. of Amigen, there was rapid death with circulatory collapse and respiratory distress. Autopsy failed to reveal any other mechanism and death was attributed to an allergic reaction to Amigen.

Ficarra[4] mentions a fatality which he attributes to Amigen administration, but he gives no essential data or circumstances, so the case cannot be evaluated.

Harris and co-workers[5] report a nonfatal case of apparent sensitivity to Amigen which occurred in a 17-year-old suicidal girl who had ingested a large amount of barbiturate. On the fourth day, a shocklike condition developed after the administration of 100 c.c. of Amigen. Recovery followed the administration of large amounts of nikethamide. It was their conclusion that Amigen may give rise to a serious allergic foreign protein reaction.

The first two case reports are not suggestive of allergic shock. Hopps and Campbell[1] are of the opinion that severely damaged livers are unable to conjugate amino acids at sufficiently rapid rates to escape acidosis and that this may be the mechanism causing death. They were unable to demonstrate antibody formation to Amigen, using rabbits. Ficarra[4] believes that sensitivity

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to a foreign protein is the underlying cause of the various reactions which may occur and advocates routine intracutaneous testing before administration. Madden and associates[6] performed a series of experiments with various amino acid solutions and casein digests and found no serious reactions. The common reactions of nausea, vomiting, and flushing were apparently related to the amount of glutamic acid present in the solution and not to any allergic manifestation.

The case history to be reported here represents, in our opinion, a true hypersensitivity reaction. This developed immediately after the administration of not more than 4 c.c. of protein hydrolysate (Amigen) and death occurred with the classical signs and symptoms of anaphylaxis within sixty minutes. By means of the Prausnitz-Küstner passive transfer test, an immediate urticarial skin reaction to Amigen was demonstrated similar to that found in atopic disorders.

CASE REPORT

C. M., a 44-year-old white man, was admitted to the hospital on July 22, 1948 with a chronic duodenal ulcer and pyloric obstruction. This condition had been present with quiescent and recrudescent periods for the past four years.

The past history, as related by the patient, was irrelevant; however, the family stated that the patient had attacks of asthma, apparently precipitated by dust. No food allergy or idiosyncrasy could be elicited. No familial history of food allergy was obtained. There was no history of previous administration of protein digests.

Physical examination revealed a well-developed, moderately well-nourished white male of stated age in no acute distress. Blood pressure was 130/80; pulse, 90; temperature, 98.6° Fahrenheit. Pain and tenderness in the right epigastrium were the only significant findings.

Laboratory tests were essentially normal, as follows: R.B.C., 4,750,000; Hb., 15 Gm.; W.B.C., 13,900; neutrophiles, 71 per cent; lymphocytes, 28 per cent; monocytes, 1 per cent; Kahn reaction, negative; urinalysis, negative; total serum proteins, 6.25 Gm. per cent; albumin, 4.34 Gm.; globulin, 1.91 Gm.; A-G ratio, 2.25; fasting gastric acidity, 40 degrees free hydrochloric acid.

X-ray findings in this hospital were equivocal regarding the presence of a duodenal deformity.

The patient was placed on a medical peptic ulcer regimen of diet, antiacids, and antispasmodics, with relief of all symptoms except nocturnal pain, which was relieved only by gastric aspirations. This program was followed for a period of six weeks when gastric surgery was decided upon. On September 8, 1949, an operation was performed using endotracheal cyclopropane anesthesia. A chronic anterior duodenal ulcer was found. A Polya type of subtotal gastric resection, with a posterior gastroenterostomy, was done. During the course of the operation 500 c.c. of citrated whole blood was given, followed later in the day by another transfusion of 500 c.c. of blood. The operative and postoperative courses were entirely uneventful, there being at no time any evidence of shock, circulatory or respiratory difficulty.

On the following morning, the patient was ambulatory and appeared to be in excellent condition. At 10:00 A.M. Amigen solution, 5 per cent in 5 per cent glucose, was started intravenously. Immediately, the patient became apprehensive and complained of difficulty in breathing. The infusion was stopped after about 4 c.c. had entered the vein. At 10:02 A.M., 0.5 c.c. of adrenalin hydrochloride (1:1,000) was given intramuscularly. The dyspnea became more marked and 100 per cent oxygen was administered through a mask. Another 0.5 c.c. adrenalin was given intravenously at 10:05 A.M. The respiratory difficulty became progressively more marked, and at 10:10 the patient was showing signs of upper respiratory

obstruction with marked inspiratory efforts, flaring of lower edge of the ribs, and suprasternal retraction. A laryngoscope was inserted for the purpose of placing an endotracheal tube, and the uvula, epiglottis, pharyngeal wall, and vocal cords were found to be extensively swollen and edematous. The glottis was closed and it was impossible to insert a tube. At this time, the patient was extremely cyanotic and respirations ceased. Artificial respiration was started and at 10:15 a tracheotomy was performed and 100 per cent oxygen given through the tracheotomy tube. No pulse could be discerned and 0.5 c.c. of adrenalin was given intracardially, after which heart action was resumed. The cyanosis gradually disappeared. Coramine, 2 c.c. intramuscularly, failed to restore respiratory function and artificial respiration was started. At this time, some spasmodic rigidity of the extremities became evident and sodium amytal, gr. 3¾ intravenously, promptly inhibited these motions. Good respiratory exchange continued for thirty minutes after the tracheotomy. It then progressively diminished and numerous moist rales developed in the lungs. Following the onset of pulmonary edema, the patient rapidly became worse and died at 11:00 A.M., one hour after parenteral administration of Amigen.

Permission for autopsy was obtained and the following pertinent findings were noted:

Brain: Multiple sections of the brain revealed cerebral congestion with prominent engorged vessels. Microscopically the small vessels were distended as were those in the pituitary gland.

Throat and Neck: The pharyngeal, laryngeal, and tracheal mucosae were pale and edematous. The vocal cords were boggy, wet, and swollen. Peritracheal and carinal lymph nodes were grossly edematous. Sections of the vocal cords showed recent hemorrhage with considerable edema and congestion of the submucosa and infiltration by large mononuclear cells, plasma cells, neutrophiles, lymphocytes, and a few eosinophils. The tracheal submucosa presented a similar picture.

Lungs: The right lung weighed 700 grams and the left lung, 640 grams. Although crepitant, considerable congestion was present, especially at the bases. Sectioning revealed wet, red-gray surfaces with dark bloody areas at the bases. The bronchial tree contained frothy red fluid. Microscopic studies revealed distended alveoli with rupture in some areas, while edema was a constant finding. The vessels were generally contracted. The bronchi and bronchioli showed contracted outlines and the lumens contained mucus, fibrin, debris, and varying amounts of blood.

Liver: The liver weighed 1,560 grams and sectioning revealed a congested, red-brown surface. Microscopic sections showed marked engorgement of the central veins and general dilatation of the sinusoids. No evidence of hepatic cell damage was present.

Spleen: The spleen weighed 130 grams. On sectioning, the pulp was firm and the trabeculations were prominent, but the corpuscles were not easily visualized. Microscopically the splenic pulp was congested and the sinuses were dilated and engorged.

Kidneys: Grossly no changes were detectable in the kidneys, but microscopic examination revealed considerable congestion of the parenchyma. The vessels were markedly dilated and engorged, especially the glomerular capillaries. The tubules were swollen and granular with their lumens containing eosinophilic albuminous material.

Gastrointestinal tract: There was edema of the submucosa of the esophagus; otherwise, aside from the recent gastric resection and gastrojejunostomy, no significant changes were found in the remainder of the gastrointestinal tract.

Lymph Nodes: Sections of cervical, peritracheal, and mediastinal lymph nodes showed edema, congestion, and early reactive hyperplasia.

Laboratory Tests.—

Prausnitz-Küstner Passive Transfer Test: The Prausnitz-Küstner test was performed using blood of the patient obtained by auricular puncture immediately after death. This blood was permitted to clot, the serum was separated and kept for twenty-four hours in the refrigerator. Then 0.1 c.c. of this serum was injected intracutaneously in the left forearm

of four normal test persons. Each person received also an intracutaneous injection of 0.1 c.c. of a normal serum in the right forearm. There was the usual slight swelling after the injection which disappeared in a very short time. The sensitized areas were encircled with ink marks. Twenty-four hours later the sensitized areas could be distinguished from normal skin by the ink marks only. At this time undiluted Amigen solution from the original flask was injected intracutaneously into the two areas and in a nonsensitized area on the right forearm. Three of the four test persons received 0.05 c.c. Amigen in each site, the fourth test person received injections of 0.1 c.c. at the described areas. Immediately after the injection of Amigen, the areas previously sensitized with the patient's serum began to itch and developed redness and swelling. This occurred in all test persons, with slightly greater severity in the person receiving the larger injection of Amigen. No significant reaction was observed at any of the two control sites of Amigen injection in any of the test persons. Only slight burning from the injection proper was noted and this disappeared within a few minutes. The reaction at the site of sensitization with the patient's serum increased in severity during the following four to six hours, then subsided gradually, disappearing completely after sixteen to twenty-four hours. In all test persons the reaction consisted of itching, swelling, and redness involving areas of approximately 7 × 10 centimeters. In addition, in two test persons wheals and pseudopods developed, persisting for about eight hours. In the test person receiving the 0.1 c.c. dose of Amigen, pain and a feeling of pressure extended into the elbow and upper arm.

Studies of Blood Donors: The patient had received two blood transfusions in the twenty-four hours prior to the administration of Amigen and to his death. The donors were available for study. One had had a severe attack of hives eighteen months before but was negative to all the usual skin tests at this time. Neither donor had ever received a blood transfusion or Amigen injection. Serum obtained from these donors gave negative passive transfer tests with Amigen. Furthermore the donors were not sensitive to the intradermal injection of Amigen.

Further attempts to determine possible antigenic properties of the Amigen used in our patient were carried on as follows:

Guinea Pig Inoculations: Four guinea pigs were given intracardiac injections of 0.5 c.c. of Amigen solution from the original flask. Ten days later two of these animals were reinjected with 0.2 c.c. of the same Amigen solution. These injections were tolerated without any reaction. The animals survived and are well at present. The two remaining animals were used on the eighteenth day after sensitization when they received intracardially 0.2 c.c. of the original Amigen solution. No anaphylactic reaction developed after these injections. The animals survived and are well.

Similar but more extensive experiments with the same lot of Amigen were carried out in the Research Laboratories of the manufacturers,* who permit us to include their observations in this report. The results confirmed our own findings. Forty test animals and fifteen control animals were used with the following results:

1. Ten guinea pigs were injected with the Amigen solution and after a three-week period were reinjected with Amigen. All responses were negative.

2. Ten guinea pigs were injected with the Amigen solution and after a three-week period were reinjected with skim milk; all responses were negative. Five control animals, sensitized and reinjected with skim milk, responded positively.

3. Twenty guinea pigs were injected with the Amigen solution and after a three-week period were injected with pancreas extract. All responses were negative. Ten control animals sensitized and reinjected with pancreas extract responded positively.

From these results it can be concluded that the involved lot of Amigen was "non-anaphylactic" to guinea pigs.

*Mead Johnson & Company, Evansville, Ind.

COMMENT

The autopsy findings are compatible with those described as occurring in anaphylactic shock. Vance and Strassman[8] state that death usually occurs due to asphyxia resulting from bronchial spasm. Autopsy findings are: inflated lungs, contraction of the bronchial musculature, and submucosal edema with infiltration by eosinophiles. Other organs such as brain and liver often show an intense congestion.

The positive Prausnitz-Küstner passive transfer test, the exclusion of a specific reagin from the transfused blood, and the failure to demonstrate in test persons and in animal experiments allergenic properties in the Amigen would indicate that the patient's serum contained a specific reagin probably dependent on a constitutional abnormality. Such an abnormality will have to be classified as an atopic sensitivity.

Lund and Hunt[7] believe that the passive transfer reaction is a reliable test for the diagnosis of hypersensitivity to a specific allergin. The diagnostic criteria of allergic shock as given by them are fulfilled in our case. (1) "The injected material was not toxic for a normal person." (2) "The symptoms produced were characteristic of an allergic state." (3) "The autopsy disclosed no other explanation of death." (4) "A specific sensitizing agent corresponding with the material injected was found in the blood serum by the technic of passive transfer."

One can only speculate as to the character of the atopic sensitivity demonstrated. If the patient had been allergic against his own pancreatic trypsin, as has been suggested, then his blood may have carried a hapten for Amigen. Thus an anaphylactic reaction might have been precipitated with a non-allergenic protein digest.

Hypersensitivity reactions to protein digests are not frequent and seldom very severe. The incidence of fatal reactions is extremely rare and is probably no higher than the risk attending intravenous administration of many other substances usually considered harmless. Yet, an experience like the one reported should call for caution and careful evaluation of the benefits and the dangers from the use of such a substance. It seems to be advisable to carry out in all patients sensitivity tests prior to the administration of protein digests. This precaution should be observed especially if an interval of time has occurred since a previous administration.

SUMMARY

1. A case of fatal allergic shock following Amigen administration is reported.

2. Passive transfer tests with the patient's serum were positive. The solution of protein hydrolysate (Amigen) used in this patient was not allergenic when tested in guinea pigs and normal persons. It is assumed therefore that the death of the patient was due to an atopic reaction.

3. It is suggested that all individuals to receive protein digests parenterally should be tested previously for sensitivity to the digest.

REFERENCES

1. Hopps, H. C., and Campbell, J. A.: Immunologic and Toxic Properties of Casein Digest as Prepared for Parenteral Administration, J. Lab. & Clin. Med. **28**: 1203, 1942.
2. Curreri, A. R., Hibma, O. V., and Cohen, P. P.: Fatality Associated With the Administration of Amino Acid Digest, J. A. M. A. **128**: 732, 1945.
3. Elman, R.: Parenteral Alimentation in Surgery, New York, 1947, Paul B. Hoeber, Inc.
4. Ficarra, B. J.: Intradermal Sensitivity Tests for Amino Acids, Am. J. Surg. **72**: 744, 1946.
5. Harris, H. J., Gordon, O. A., Gray, R., and Barton, L. G.: Apparent Sensitivity to Amigen, J. A. M. A. **132**: 785, 1946.
6. Madden, S. C., Woods, R. R., Shull, F. W., Remington, J. H., and Whipple, G. H.: Tolerance to Amino Acid Mixtures and Casein Digests Given Intravenously; Glutamic Acid Responsible for Reactions, J. Exper. Med. **81**: 439, 1945.
7. Lund, H., and Hunt, E. L.: Postmortem Diagnosis of Allergic Shock; Value of Prausnitz-Küstner Reaction, Arch. Path. **32**: 664, 1941.
8. Vance, B. M., and Strassmann, G.: Sudden Death Following Injection of Foreign Protein, Arch. Path. **34**: 849, 1942.

FAILURE OF RAGWEED POLLEN EXTRACT TO DESTROY WHITE CELLS FROM RAGWEED-SENSITIVE PATIENTS*

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THE cells of various tissues are of extreme importance in hypersensitivity. The difference between allergic and nonallergic individuals must fundamentally arise in the cells. Furthermore, although it is still not entirely clear just which cells are responsible for antibody production, one or more types are the site of formation. Because of the comparative ease with which they are done, however, serological reactions and skin tests have been the chief concern of immunologists and allergists, rather than a study of cellular reactions in vitro or in tissue culture.

In those forms of allergy, such as tuberculin and contact types, where serological reactions have been difficult to demonstrate, the least quantitative information exists. However, altered cellular reactions have been demonstrated. Landsteiner and Chase[1, 2] showed that cells of a peritoneal exudate from animals with tuberculin or contact type hypersensitivity, when injected intra-abdominally, were able to confer transitory sensitivity to normal animals. Favour[3, 4] showed that white blood cells from animals and patients with tuberculosis and certain other infections could be destroyed in vitro by products of the infecting organism. These phenomena may prove useful in studying this type of hypersensitivity. When it was reported in this journal[5] that a similar effect may be produced by the in-vitro mixing of ragweed extract with blood from ragweed-sensitive patients, it seemed that this might provide an additional method of studying atopic allergy, and, consequently, it was thought advisable to repeat this work.

METHODS

The method used is that of Squier and Lee[5] with modifications designed to improve the accuracy of counting. Five cubic centimeters of blood was drawn into a mineral-oil-coated syringe containing 0.25 c.c. of heparin (liquaemin Roche, 10 mg./c.c.) and 0.1 c.c. of 5 per cent glucose. The blood was mixed with anticoagulant, and then 2.5 c.c. portions were delivered into each of two test tubes. To one tube 0.1 c.c. of a 1:40 ragweed pollen extract made up in unbuffered saline adjusted to pH 7.4 was added. To the control tube 0.1 c.c. of unbuffered saline was added. The tubes were thoroughly mixed (three minutes in a mechanical agitator), and samples were withdrawn for enumeration of white cells. The tubes were then allowed to stand for one hour at room temperature, at which time they were again agitated for three minutes, and samples were taken for a second count. If there were destruction of white cells by ragweed, the drop in count in the tube with ragweed pollen extract should be greater than the drop in the saline control.

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In each instance, counts were done using a standard white cell diluting pipette, the pipette being filled to the 0.5 mark with blood and then filled to the 11 mark with 2 per cent acetic acid. Meticulous care was taken in filling the pipettes, which was done with a hand-operated, screw-type suction device. After filling, the pipettes were agitated for three minutes in a mechanical shaker, and the mixed white cell suspension was then counted in a Fuchs-Rosenthal (0.2 mm. deep) counting chamber. An entire side of the chamber, 16 sq. mm., containing an average of approximately 1,000 cells, was counted. This was done in order to reduce the sampling error inherent in counting techniques. Even with these precautions, it was impossible to reproduce counts more closely than about 5 per cent to 10 per cent on the same blood sample.

Seven untreated patients with clear-cut ragweed sensitivity were used in this study. All the patients had endermal reactions to ragweed and had symptoms of either hay fever or asthma during the ragweed season. Serum from each subject, diluted 1:5, conferred skin sensitivity to ragweed pollen extract in a normal recipient. In six patients, two tests were done at different times, and in one patient only one test was carried out.

RESULTS

The results are shown in Table I, which includes all counts done in this study. It will be noted that in no instance was the drop in white count significantly greater in the tube containing ragweed pollen extract than in the tube containing saline. In one instance there was a drop of 26 per cent in the tube with saline and no significant drop in the tube with ragweed. This result is probably due to an error. An increase in count at the end of one hour over the immediate count, which was observed in eleven instances, can only be due to the error inherent in counting. In some instances, fairly large and consistent drops took place in both the tube with ragweed and the tube with saline. This probably represents a nonspecific destruction of white cells on standing and is frequently observed in carrying out tests such as these. Why it should occur in some individuals and not in others is unexplained.

DISCUSSION

The results obtained do not indicate any increase in destruction by ragweed pollen extract of white blood cells obtained from ragweed-sensitive individuals. This is in disagreement with a report by Squier and Lee,[5] in which a pronounced and consistent reduction of such cells on exposure to ragweed occurred. It is difficult to account for this discrepancy. The most important error in the enumeration of white cells is that due to an inadequate sample. Whether or not this may account for the discrepancy cannot be ascertained from their report, because the details of the counting technique are not given. In the usual technique of counting white cells, in which a chamber 0.1 mm. deep is used and four 1 mm. squares are counted, the total number of cells enumerated is usually about 100 to 200. It has been estimated[6] that when this number of cells is counted, even with the utmost care, the error in duplicate

TABLE I

PATIENT	DIAGNOSIS	DATE OF TEST	TOTAL NUMBER CELLS COUNTED IN 16 SQ. MM. 0.2 MM. DEEP*				% CHANGE	
			RAGWEED TUBE		CONTROL TUBE		RAGWEED TUBE	CONTROL TUBE
			IMMEDIATE	ONE HOUR	IMMEDIATE	ONE HOUR		
1	Ragweed	9/29/48	982	971	932	925	− 1.2	− 0.8
	Hay fever	10/22/48	1,122	1,183	1,198	1,261	+ 5.4	+ 5.3
2	Ragweed	9/30/48	1,062	936	874	790	−12.0	− 9.6
	Hay fever	10/20/48	1,261	1,060	1,075	955	−15.9	−11.2
3	Ragweed	10/ 1/48	1,041	1,058	992	996	+ 1.5	+ 0.3
	Hay fever	10/27/48	929	994	1,026	1,005	+ 6.8	− 2.0
4	Ragweed	9/30/48	536	562	740	545	+ 4.7	−26.0
	Hay fever	10/21/48	975	986	926	982	+ 1.1	+ 6.0
5	Ragweed	10/ 6/48	734	704	746	678	− 4.0	− 9.1
	Hay fever	10/29/48	678	540	740	643	−20.3	−13.1
6	Ragweed	10/13/48	1,135	1,059	1,095	998	− 6.7	− 8.8
	Asthma	10/30/48	1,184	1,236	1,295	1,157	+ 4.4	−10.7
7	Ragweed	10/28/48	909	1,030	893	1,001	+11.7	+10.8
	Hay fever							

*To obtain cells per cu. mm of blood, multiply by 6.95.

samples may be as much as 20 per cent. With our technique, the error is reduced to about 5 per cent to 10 per cent, but elimination of all error is a practical and theoretical impossibility. Since this variation can be in either direction, the reason for a rise in some counts after an hour is clear. It is difficult to account for the lack of rise in any of the controls of Squier and Lee, unless an unknown factor was responsible for the destruction of cells in the control tubes. Whether or not these considerations account for the difference in reported results is not clear.

SUMMARY

1. An attempt to confirm the previous observation that ragweed pollen extract destroys in-vitro white blood cells from ragweed-sensitive patients was unsuccessful.

2. In none of the thirteen tests on seven ragweed-sensitive patients did a greater destruction of cells occur upon addition of ragweed pollen extract than upon addition of saline.

REFERENCES

1. Landsteiner, K., and Chase, M. W.: Experiments on Transfer of Cutaneous Sensitivity to Simple Compounds, Proc. Soc. Exper. Biol. & Med. **49:** 688, 1942.
2. Chase, M. W.: The Cellular Transfer of Cutaneous Hypersensitivity to Tuberculin, Proc. Soc. Exper. Biol. & Med. **59:** 134, 1945.
3. Favour, C. B.: Lytic Effect of Bacterial Products on Lymphocytes of Tuberculous Animals, Proc. Soc. Exper. Biol. & Med. **65:** 269, 1947.
4. Favour, C. B.: Personal communication.
5. Squier, T. C., and Lee, H. J.: Lysis in Vitro of Sensitized Leukocytes by Ragweed Antigen, J. ALLERGY **18:** 156, 1947.
6. Berkson, J., Magath, T. B., and Hurn, M.: The Error of Estimate of the Blood Cell Count as Made with Hemocytometer, Am. J. Physiol. **128:** 309, 1940.

THE INFLUENCE OF TEMPERATURE VARIATIONS AND WINDS ALOFT ON THE DISTRIBUTION OF POLLENS AND MOLDS IN THE UPPER ATMOSPHERE

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IT HAS been pointed out previously that pollen grains and mold spores may concentrate in clouds and that the level of maximum concentration rises during the day and falls at night.[1] The purpose of this paper is to explain the mechanism which is responsible for the vertical migrations of pollen grains and mold spores.

Ordinarily the temperature of the air falls with increasing altitude. The rate of temperature change with altitude is known as the lapse rate and is about 5½° F. per 1,000 feet or 1° C. per 100 meters of altitude for dry air and about one-half of that rate for moist air. The reason for this difference is that moist air becomes warmer when its water vapor changes to the liquid phase, since the latent heat of condensation is added to the air temperature. A high lapse rate is usually associated with unstable air since the lighter, warmer air rises by convection into the heavier, colder air above. On the other hand, a low lapse rate occurs in stable or smooth air, since the upward currents cease when the upper layer of relatively warm air forms a barrier to the rise of air. The importance of the lapse rate is illustrated by the vertical sampling of the air. The method used is described in a previous paper.[1] All counts represent the number of particles impinging on 1 sq. cm. of a slide exposed from the side of a plane traveling at an indicated air speed of 90 m.p.h. for five minutes.

RESULTS

Although vertical surveys of pollens were made almost daily during the fall hay fever season of 1948, only a few of the characteristic findings will be shown in tabular form.

TABLE I

	WINDS ALOFT		
	ALT.	DIRECT.°	M.P.H.
Aug. 12, 1948; High broken clouds;	7,000	50	08
Ceiling, 8,000 feet; Visability, 10 mi.;	6,000	40	07
Barometer, sea level, 29.89;	5,000	120	05
Temp. 73°; Dew point, 60;	4,000	360	02
Wind, ENE, 14; Time, 1600	3,000	160	06
	2,000	150	10
	1,000	140	14

Wind shift with mild wind—no effect on solid particles.

ALT. FEET	TEMP. F.	ALTERNARIA (A)	RAGWEED (R)
6,500	42	40	10
5,500	55	125	30
4,500	60	95	40
3,500	65	175	25
2,500	71	125	25
1,500	75	95	35

Gravity, 24-hour slide
Alternaria 4, Ragweed 1

This table illustrates the effect of turbulent air having an unusually high lapse rate. It is also interesting to note the discrepancy between the airplane survey of particles compared to the gravity method.

TABLE II.

	WINDS ALOFT		
	ALT.	DIRECT.°	M.P.H.
Aug. 13, 1948	7,000	180	18
Ceiling, unlimited; Visability, 10 mi.;	6,000	180	20
Barometer, 29.98;	5,000	190	17
Temp. 72°;	4,000	190	12
Wind, E, 12; Time, 1345	3,000	150	17
	2,000	140	22
	1,000	140	16

Wind shift below 4,000 feet—doubtful effect.

ALT. FEET	TEMP. F.	ALTERNARIA (A)	RAGWEED (R)
6,500	51	0	0
5,500	52	45	9
4,500	55	95	15
3,500	60	145	10
2,500	65	275	0
1,500	58	85	5

Gravity, 24-hour slide
Alternaria 10, Ragweed 4

High lapse rate decreasing suddenly at 5,500 feet. This level forms a barrrier to further rise of solid particles.

TABLE III.

	WINDS ALOFT		
	ALT.	DIRECT.°	M.P.H.
Aug. 18, 1948	7,000	320	21
Ceiling, 6,000 feet; Visability, 9 mi.;	6,000	330	21
Barometer, sea level, 29.91;	5,000	330	22
Temp. 78°; Dew point, 61;	4,000	330	18
Wind, NE, 8; Time, 1545	3,000	330	17
	2,000	350	10
	1,000	30	07

No radical changes above 2,000 feet—no pollen barrier.

ALT. FEET	TEMP. F.	REMARKS	ALTERNARIA (A)	RAGWEED (R)	RUST	TIME
9,500	43	above clouds	2	1	0	1550
8,500	40	in clouds	75	15	1,400	1600
7,500	43	in clouds	125	40	900	1605
6,500	47	below clouds	170	125	900	1615
5,500	53	below clouds	110	60	1,200	1625
4,500	58	below clouds	120	95	700	1630
3,500	65	below clouds	115	70	900	1635
2,500	70	below clouds	205	90	1,100	1643
1,500	72	below clouds	135	180	1,200	1650

Gravity, 24-hour slide
A, 0; R, 0; Rust, 100

High lapse rate decreasing at cloud level. Temperature inversion above clouds. Low gravity count attributed to high altitude of pollens.

TABLE IV.

	WINDS ALOFT		
	ALT.	DIRECT.°	M.P.H.
Aug. 19, 1948	9,000	20	17
Ceiling, unlimited; Visability, 10 mi.;	8,000	20	13
Temp. 73°; Dew point, 59;	7,000	20	11
Wind, E, 9; Time, 1600	6,000	40	09
	5,000	60	05
	4,000	10	11
	3,000	20	07
	2,000	40	09
	1,000	40	10

Mild winds—not much change in direction.

ALT. FEET	TEMP. F.	ALTERNARIA (A)	RAGWEED (R)	RUST
8,500	52	0	0	0
7,500	55	4	0	0
6,500	56	2	0	0
5,500	57	1	0	0
4,500	57	50	5	90
3,500	62	40	10	40
2,500	70	125	90	700
1,500	70	120	70	120

Gravity, 24-hour slide
A, 20; R, 0; Rust, 10

High lapse rate up to 4,500 feet; barrier to further rise of ragweed and rust when lapse rate becomes 0.

TABLE V.

	WINDS ALOFT		
	ALT.	DIRECT.°	M.P.H.
Aug. 20, 1948	7,000	130	01
Ceiling, unlimited; Visability, 12 mi.;	6,000	160	07
Barometer, 30.07;	5,000	170	08
Temp. 76°; Dew point, 63;	4,000	170	25
Wind, SE 9; Time, 0945	3,000	180	15
	2,000	180	12
	1,000	170	09

Wind decreases above 4,000 feet corresponding to pollen barrier.

ALT. FEET	TEMP. F.	ALTERNARIA (A)	RAGWEED (R)	RUST	
6,500	60	0	0	5	Air
5,500	61	5	0	15	smooth
4,500	61	5	0	25	
3,500	61	185	160	700	
2,500	66	250	160	700	Air
1,500	71	185	105	400	turbulent

Gravity, 24-hour slide
A, 25; R, 75; Rust, 55

When lapse rate becomes 0 the turbulence of the air subsides and further rise of pollen is halted.

TABLE VI.

	WINDS ALOFT		
	ALT.	DIRECT.°	M.P.H.
Sept. 15, 1948; Clear;	9,000	310	37
Ceiling, unlimited; Visability, 12 mi.;	8,000	310	36
Temp. 85°; Dew point, 59;	7,000	310	29
Wind, SW, 21 to 30; Time, 1445 to 1515	6,000	310	25
	5,000	300	20
	4,000	270	21
	3,000	260	17
	2,000	240	19
	1,000	220	20

No great changes.

ALT.* FEET	TEMP. F.	ALTERNARIA (A)	RAGWEED (R)	RUST	REMARKS	TIME
8,500	54	15	0	0	water droplets +++ on slide	1504
7,500	57	1	3	10	water ++	1511
6,500	58	7	4	0	water +	1518
5,500	61	235	125	10	water +	1525
4,500	66	290	180	235		1532
3,500	71	305	180	60		1538
2,500	75	225	210	245		1545
1,500	82	245	200	0		1552

*Haze layer ends at 7,500 feet at which level are greatly scattered cumulus clouds.

The usual decrease in the number of particles above the level where the lapse rate changes from the dry air type to the moist air type is illustrated. Additional confirmation of condensation is obtained by the water droplets on the slides at and above 5,500 feet. Note also that the dew point at ground level approximates the temperature at which condensation occurs.

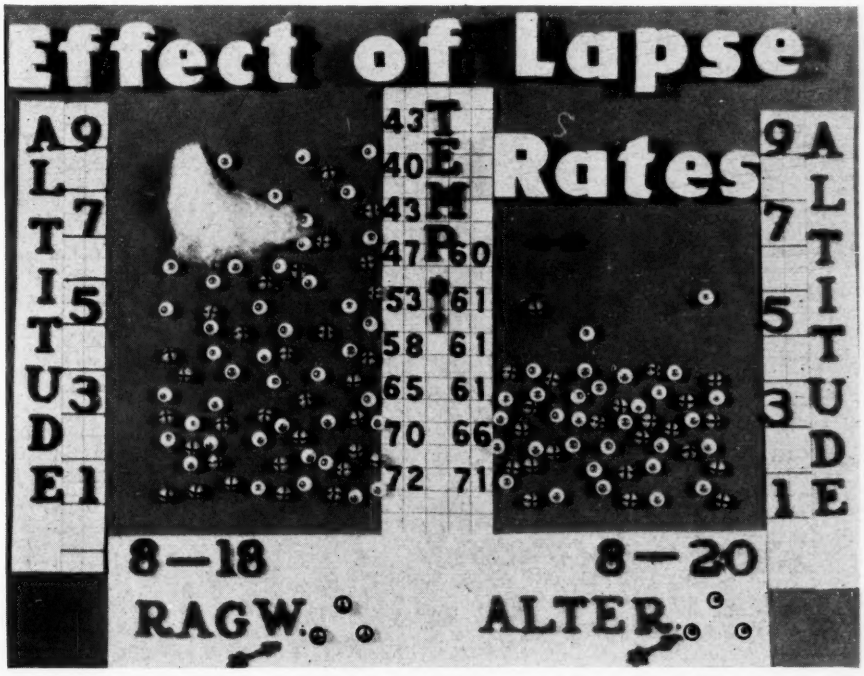

Fig. 1.—Numbers at the sides of the diagram indicate thousands of feet of altitude. Numbers at the center are temperatures on the Fahrenheit scale. High lapse rate on August 18 associated with high dissemination of pollen. On August 20, the temperature failed to rise above 3,500 feet and this condition is associated with a barrier to the further rise of pollens and molds.

COMMENT

Pollen grains and mold spores rise into the upper atmosphere to a height which depends chiefly upon the lapse rate. A high lapse rate is usually associated with turbulent air and a high dissemination of particles. At the level where the lapse rate becomes low, the solid particles are prevented from rising. These facts explain the vertical migration of pollens described in a previous paper. The influence of winds aloft on the concentration of solid particles is of minor importance compared to the lapse rate. The information obtained has been of value in prophesying pollen counts twenty-four hours in advance. Further studies are being directed toward the prophesying of pollen counts and the collection of data regarding geographic distribution.

Some unusual epidemics, such as the Donora incident of 1948, can be explained on the basis of lapse rates.

We are indebted to the United States Government Weather Bureau of Milwaukee, Wisconsin, for their aid in supplying meteorological data.

REFERENCE

1. Heise, H. A., and Heise, E. R.: The Distribution of Ragweed Pollen and Alternaria Spores in the Upper Atmosphere, J. ALLERGY **19**: 403, 1948.

SYMPTOMS OF HAY FEVER CAUSED BY ALGAE

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ALL allergists are familiar with the individual whose hay fever is aggravated by swimming in lakes and rivers. However, there are some persons who do not have ordinary hay fever but who are so affected by outdoor swimming that they are constrained from continuing this activity.

CASE REPORTS

Case 1.—H. H., a 57-year-old man, had catarrh in childhood, migraine caused by chocolate and milk most of his life, and frequent sinus infections. He swam daily during the summer months in North Lake, Waukesha County, Wis., from 1900 to 1917 without discomfort, and from 1917 to 1934 in swimming pools and in a Pennsylvania mountain lake without symptoms.

Late in August, 1934, three hours after swimming in weedy Muskego Lake, Waukesha County, Wis., itching of the eyes and complete blockage of the nose occurred which cleared up within 48 hours. Late in August, 1935, after swimming in the same lake the same train of events occurred, but this time there was in addition some mild asthma.

From 1936 to 1946 the patient swam in North Lake during the summers. He had no trouble until about August 15 each year, when swimming was followed by nasal discharge and blockage, conjunctivitis, and slight asthma. Skin tests were negative for pollens and other inhalants, but positive for milk and chocolate. In spite of negative pollen tests, preseasonal and coseasonal treatment was given for ragweed, marsh elder, cocklebur, sage, mugwort, pigweed, Russian thistle and molds. This treatment was carried on from 1940 to 1944 and was without effect.

On Aug. 12, 1944, some floating green scum was collected at the shore of North Lake. Extracts gave immediate skin reactions in dilutions up to 1:100,000 and passive transfer tests were positive. When an intracutaneous injection of .03 c.c. of 1:1,000 dilution was administered, slight asthma occurred within 20 minutes and the site of injection reached its maximum swelling measuring 4 cm. in diameter in 4 hours. Control tests were made on normal individuals without local or focal reactions. Intracutaneous injections beginning with 0.3 c.c. of the 1:100,000 dilution were administered at weekly intervals from June to September for four seasons (1945-1948). The maximum dose was 0.3 c.c. of a 1:10,000 dilution. This treatment was followed by almost complete relief from eye and nasal symptoms and there was no more asthma. Swimming could again be enjoyed without discomfort.

THE ANTIGEN

The material collected consisted chiefly of *Schizophyta,* Class: *Myxophyceae,* or blue-green algae. Subgroup *Oscillatoriaceae* represents the commonest inhabitant of the scum. These plants known as "water bloom" are often responsible for discoloration of the water. Furthermore, the bloom may be responsible for the death of fish, and the water has been known to be injurious to livestock drinking it.[1]

An interesting observation of the fresh material is the spontaneous movement of the strands of *Oscillatoriaceae.* The movement is startling when first observed. There is either a waving or a whiplike movement or a forward and backward motion of the strand on its own axis.

Fig. 1 was made from the formaldehyde-preserved scum two and one-half years after the algae had been collected. In order to evaluate the antigenic

concentration of this preserved material, which had been kept at room temperature, some of it was dried at 37.5° F. and found to contain 0.25 per cent of solids. On the basis of this information, dilutions from 1:1,000 to 1:1,000,000 were prepared. The original formaldehyde-preserved material was dialyzed, the outside water containing calcium hydroxide in order to destroy the formaldehyde. The material remaining after dialysis was brought up to its original volume with glycerosaline. Dilutions of this 0.25 per cent extract were made in Unger's solution.

Fig. 1.

Further experiments with this antigen indicated that most individuals failed to react to intracutaneous injections, but many individuals who knew that swimming caused symptoms of hay fever reacted to dilutions up to 1:100,000.

Case 2.—J. H., a 39-year-old woman had fall hay fever and seasonal asthma most of her life. Positive skin reactions were secured to ragweed, molds, dust, and feather extracts. In spite of treatment which was continuous since 1943 she had severe symptoms when vacationing at Lake Keesus in Waukesha County, Wis. However, she had much less trouble when living in Milwaukee.

On Sept. 1, 1945 while swimming in Lake Keesus her eyelids became swollen until the eyes were closed, her nares closed, and an urticarial eruption covered her body from

head to feet. About one week later a skin test of .03 c.c. of 1:10,000 dilution of algae antigen was followed by an immediate local reaction which was so severe that epinephrine was injected into the skin-testing site. No treatment was given for the algae allergy since the patient was convinced that she would never swim there again. However, on Aug. 10, 1946, she again swam in Lake Keesus and the same symptoms ensued.

SUMMARY

1. A potent antigen was prepared from algae growing in a lake in Waukesha County, Wis.

2. This antigen elicited positive skin tests in an individual whose symptoms of hay fever were aggravated by swimming in that lake and in an individual who did not have pollinosis, but who likewise developed symptoms of hay fever.

3. Positive passive transfer tests to algae extract were obtained from one of the two patients.

4. The antigen was effective in the treatment of this allergic condition.

5. A specimen of algae preserved in formaldehyde retained a high titer of antigenicity for two and one-half years.

REFERENCE

1. Smith, G. M.: The Fresh-Water Algae of the United States. New York and London, 1933, McGraw-Hill Book Co., Inc., p. 39.

A DYE INCORPORATING RAPID PERMANENT POLLEN MOUNTING METHOD*

JOHN E. NEWLAND, M.D., CHICAGO, ILL.

A PERMANENT collection of pure pollen samples can be of great help to the allergist in identifying unknown pollens. Such a collection can be easily stained and permanently mounted in a single operation by using a plastic, polyvinyl alcohol, incorporating a dye.

Lubkin and Carsten[1, 2] described the use of grade RH-393 polyvinyl alcohol in dehydration in histologic embedding; Downs[3] described its use as a medium for mounting and clearing biologic specimens. Huber and Caplin[4] in 1947 described its use in preserving fungi and small arthropods. Working with a synthetic polymer of vinyl alcohol, Elvanol 71-24, it was found that pollens could be permanently mounted and simultaneously stained in a single operation by the use of the following:

1. Stock solution Elvanol	80%
2. Glycerin N. F.	20%
3. Basic fuchsin solution	5 to 10 drops to 100 c.c. of the above mixture

The stock solution of Elvanol as prepared by Downs[3] employs 15 Gm. of the powder added to 100 c.c. of cold water, heating gently to approximately 80° C. in a water bath. Filtering is generally necessary and crinoline made from Kings Guard gauze grade 32 × 28 of Federal specification CCC-G-101 (Millburn Mills) was found to be excellent. Air bubbles were dispelled by gently reheating the solution. The basic fuchsin solution was prepared by adding 0.2 Gm. of the dry powdered dye to 100 c.c. of water.†

In the actual mounting process it is important that the slides and coverslips be free from all grease. Pollen grains are placed on the slide by gently tapping the stopper of a pollen bottle. A drop of the stained plastic is carefully mixed with the pollen grains, and after twenty to thirty seconds, a coverslip, preferably of No. 2 thickness, is applied so that no air bubbles are trapped. The finished slides must be left standing flat for several days in order that sufficient hardening takes place before storage in a slide box. Examination of slides so prepared at the end of six months revealed no fading or separation of the coverslip.‡

*From the Allergy Unit of the University of Illinois College of Medicine and Pharmacy.

†The dye used was obtained from Coleman and Bell Co., CI No. 677.

‡A preparation incorporating 56 per cent stock solution of Elvanol, 22 per cent each of lactic acid and phenol (Downs, 3) and acid fuchsin, 0.05 per cent, as the dye proved disappointing because of the gradual fading of the stained pollens within three months. Without the dye, this preparation is excellent for mounting unstained pollens.

SUMMARY

A rapid method of mounting and staining pollens by means of a plastic, Elvanol 71-24 incorporating a basic fuchsin stain, has been described.

I wish to express my thanks to Dr. Ralph F. Voigt for supplying the pollens used in this study, Mr. Oren Durham for appraising the mounts, and to E. I. Du Pont de Nemours & Co. for furnishing the Elvanol.

REFERENCES

1. Lubkin, V., and Carsten, M.: Elimination of Dehydration in Histologic Technique, Science **95**: 633, 1942.
2. Lubkin, V., and Carsten, M.: Dehydration in Histologic Embedding Eliminated by the Use of a Water Soluble Synthetic Plastic, Arch. Path. **38**: 229, 1944.
3. Downs, W.: Polyvinyl Alcohol: A Medium for Mounting and Clearing, Science **97**: 539, 1943.
4. Huber, W. C., and Caplin, S. M.: Simple Plastic Mount for the Preservation of Fungi and Small Arthropods, Arch. Derm. & Syph. **56**: 763, 1947.

Editorial

Reprint From the Annals of Internal Medicine, June, 1949, Issue

Graduate Education in Allergy

IN A RECENT survey of hospital and medical college residencies and fellowships in allergy conducted by the Subcommittee on Graduate Education of the American Academy of Allergy it was found that 17 institutions in the United States offer facilities for this type of training. Of this group eight stated that it was difficult to attract high grade men. A consideration of this problem furnishes the basis of this report.

There would seem to be several reasons for this situation. Ignorance of the opportunities available for research and clinical training in allergy is one. Failure of the present facilities to attract is another. It is also probable that our courses in medical schools underemphasize the importance of allergic diseases,[1] and as Barr[2] says, "it is more than deplorable that many young internists have been permitted to finish their training without contact with

GRADUATE EDUCATION IN ALLERGY (FELLOWSHIPS AND RESIDENCIES)

	COUNCIL APPROVED	NUMBER	FILLED	TOTAL TRAINED
1. Brooklyn Jewish Hospital	yes	3	2	10
2. Duke University Hospital	—	1	1	—
3. Johns Hopkins Hospital	yes	1	1	11
4. Mass. General Hospital (Harvard)	yes	1	0	9
5. Michigan University Hospital	—	3	3	12
6. Milwaukee County Hospital (Marquette)	yes	1	1	—
7. Montefiore Hospital (Pittsburgh)	yes	1	1	3
8. New York Hospital (Cornell)	—	1	1	2
9. Northwestern University	yes	2	1	2
10. Roosevelt Hospital	yes	2	2	7
11. University Hospital (N. Y. University)	yes	2	2	6
12. University of Illinois	yes	4	2	2
13. University of Pennsylvania Hospital	—	1	1	—
14. University of Virginia Hospital	yes	3	3	9
15. Veterans Hospital (Aspinwall, Pa.)	yes	2	2	2
16. Virginia Medical College	yes	2	2	2
17. Washington University (Barnes Hospital)	—	1	0	1
	12	31	25	78

allergy and allergic thought." This is particularly true since few hospitals rotate their internes and assistant residents through the allergy clinic. The result has been that our best internes and residents, casting about for a field in which to do special study, have not had enough contact with the allergic diseases to be interested in them.

The table indicates the 17 hospitals and medical schools where fellowships and residencies in allergy are available. Of these, 12 have been approved by the Council on Medical Education and Hospitals of the A. M. A. and of the balance, four have applications in process. Twenty-five out of 31 openings are filled and the physicians trained through these facilities now number seventy-eight. The term in most instances is one year, generally renewable for one or two more years and the monthly stipend ranges from $50 to $280. In all cases there is close contact with the departments of Medicine or of Pediatrics and with the departments of Oto-Rhinology and of Dermatology. Opportunities for research are available and the resident is encouraged to interest himself in the basic sciences of Immunology and Bacteriology.

[1]Swineford, Oscar, Jr.: Undergraduate education in Allergy, Jr. Assoc. Am. Med. Coll., 1946, xxi, 265-270.

[2]Barr, D. P.: The relationships of allergy to medicine, Jr. Allergy, 1945, xvi, 61.

The individual pattern of the allergy services varies considerably. At the Brooklyn Jewish Hospital and at the Milwaukee County Hospital (Marquette) the residents live in the hospital, have the duties and responsibilities usually associated with a house officer, provide consultations on other services and attend the allergy clinic. At the University of Michigan Hospital, the residents in allergy are selected from the assistant resident and resident staff after three years of training in internal medicine or pediatrics. They serve as residents in allergy for two years, having the supervisory duties of a house officer and engaging in research and in undergraduate teaching. They have close contact with the general medical staff, the department of infectious diseases and the various specialty departments. At the University Hospital, New York (formerly the N. Y. Post-Graduate Hospital), the resident in allergy has charge of all allergy cases admitted from the adult allergy clinic and engages in research, the activities of the Allergy Clinic and related departments, and is also assigned to the department of Immunology and Bacteriology for additional work. He is required to continue his contact with internal medicine by attending medical out-patient clinics and conferences. The same program is in most respects followed by the Montefiore Hospital (University of Pittsburgh), University of Virginia Medical College Hospital, the Veterans Hospital (Aspinwall) and Virginia Medical College.

In a number of institutions the work is more characteristic of a research fellow with added training in clinical medicine, the specialties related to allergy and the fundamental departments of Immunology and Bacteriology. In these institutions there is less clinical responsibility on the in-patient services, the emphasis being placed upon research. Barnes Hospital (Washington University), Duke University Hospital, Johns Hopkins Hospital, Massachusetts General Hospital (Harvard), New York Hospital (Cornell), Northwestern University Medical College, Roosevelt Hospital (New York), University of Illinois, and University of Pennsylvania Hospital, follow this pattern. Some of these institutions offer post-graduate education and in this group the University of Illinois and the University Hospital of New York University are examples.

In spite of these well integrated and well planned programs, the opportunities are not attracting many high grade men. The development of graduate education in allergy is only a small part of the problem of graduate education in general. The relative absence of organization of the graduate educational facilities in our hospitals and medical schools, as compared with the courses developed for undergraduate and post-graduate education, is recognized by the Commission on Graduate Education.[3] Under graduate medical education and post-graduate courses are largely supported by student fees and university endowments, whereas education at the resident and fellowship level is for the most part dependent upon grants for special projects. Most hospitals have trouble enough to meet their necessary expenses without appropriating additional funds for what primarily amounts to an educational program. The donors of funds have placed too much emphasis on research in the laboratory and too little, especially in the field of allergy, on the development of young men whose training is primarily clinical. It is rather paradoxical to see large endowments of medical schools devoted to the training of future physicians carefully selected for outstanding qualities of leadership and then, having provided such a preëminent educational experience, fail to establish opportunities for hospital or fellowship training in which these qualities for leadership can be activated for outstanding service.

It is important to discourage undue specialization, but it is also true, especially in internal medicine, that no physician can know completely the ramifications of its important subdivisions notably allergy, infectious diseases, psychosomatic medicine, cardiology, peripheral vascular disease, hematology, metabolism, endocrinology and the special diseases of the lungs and gastrointestinal tract. Instead of leaving to chance the selection by residents and fellows of one of these smaller divisions, would it not be the part of wisdom and foresight for the leading medical institutions to group these various specialties and organize them for graduate education? Allergy would fit well into a group comprising also infectious diseases, im-

[3]Graduate Medical Education, Report of the Commission on Graduate Education, 1940, Univ. of Chicago Press, page 14.

munology and psychosomatic medicine. Similar associations comprising cardiology, peripheral vascular disease and hematology, or metabolism and endocrinology, are desirable and are necessary if young men are to be trained in strategic centers for leadership in teaching, research and consultation practice.

In the future development of allergy, emphasis will be placed on the widening scope of hypersensitivity in disease, not only to include the common allergic ailments but also the wide variety of tissue changes due to sensitization as exemplified by the researches of Landsteiner, Rich, Klemperer and others. The young man choosing allergy as a subspecialty will consider himself a part of the whole field of applied immunology. Yet, fundamentally, as Cooke[4] points out, "Education in allergy must be based upon and follow a thorough training in the broad field of internal medicine or pediatrics." To divert the resident or fellow into allergy without such preliminary training will defeat the prime purpose of graduate education in allergy, which is to furnish for teaching, research and practice, men who will not only be familiar with the concepts of hypersensitivity and immunology but will also understand their clinical application.

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and
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[4]Cooke, R. A.: Allergy in relation to medical education, Clinics, 1946, v, 322.

Correspondence

Chicago, Ill.
July 15, 1949

To the Editor:

In a paper on "Quantitative Studies in Skin Testing. I(A)" (J. ALLERGY **19:** 115, 1948), I stated that many of the criticisms leveled at skin testing as a measure of activity of allergenic extracts were due to an ". . . implicit belief that the response must be a linear function of dose." In this statement I referred to the work of Efron and Dorfman: "Studies With Antigens" (J. ALLERGY **9:** 464, 1937).

I wish to point out that the data which Efron and Dorfman presented in the work cited clearly demonstrated the nonlinear relationship between dose and response to allergenic extracts. I regret that this fact was obscured by the unfortunate wording of my sentence.

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Book Reviews

EXPERIMENTAL IMMUNOCHEMISTRY, by Elvin A. Kabot, Ph.D., and Manfred M. Mayer, Ph.D., Springfield, Ill., 1949, Charles C Thomas, Publisher, pp. 551, illustrated.

This book should belong to those interested in immunological research, so much of which is oriented to immunochemistry. One, therefore, requires a modern treatise on methodology. This text contains descriptive methods documented by adequate references.

Of particular interest to the investigative allergist is a 24-page chapter, "Anaphylaxis and Allergy," which deals with current theories and conventional experimental methods. However, since the symptomatic expression of allergy is mediated by immune reactions, one will find in this treatise present concepts of antigens and antibodies and how they unite. Thus the close relationship between allergy and immunity becomes revealed in terms of experimental procedures.

As a reference book, it is invaluable.

HANDBOOK OF DISEASES OF THE SKIN, by Richard L. Sutton, M.D., and Richard L. Sutton, Jr., M.D., St. Louis, 1949, The C. V. Mosby Co., pp. 719, illustrated.

This is an over-all textbook, well arranged, with excellent illustrations. Allergy is treated first in a chapter on "Physiology" in which fundamental concepts are given. Human allergy is finally tabulated over two pages. The effort to be complete and include many questionable situations without emphasis deprives the reader of focal points, and leads to confusion.

However, in the exposition of such lesions as contact dermatitis and other allergic skin disorders, the approach is quite opposite. Meticulous details documented by good illustrations are given. History taking is presented by a long verbatim conversation between the doctor and the patient. In this case it is effective didactic teaching in that it brings out the approach of the dermatologist who is confronted with a lesion with apparent absence of specific contactants in a case of obvious contact dermatitis. Other allergic skin disorders are treated adequately and references are ample.

CLINICAL ALLERGY, by Louis Tuft, M.D., ed. 2, Philadelphia, 1949, Lea & Febiger, pp. 690, illustrated.

The first edition of this book, published over ten years ago, was one of the most widely read works on allergy. It was oriented to the clinician but exposed fundamental concepts with clarity. Practical details were well arranged, the book was carefully indexed, and it contained references that were more than adequate. Above all, it was written by a distinguished allergist.

A second edition is timely, and the material has been brought up to date with new chapters, discussion of antihistamine therapy, endocrine aspects of allergy, and the place for chemotherapy, etc. And yet when one compares these two editions, he is confronted with the fact that insofar as clinical allergy is concerned, progress has been slow.

This book has lost none of its excellence in its revision and is highly recommended as a text and a reference.